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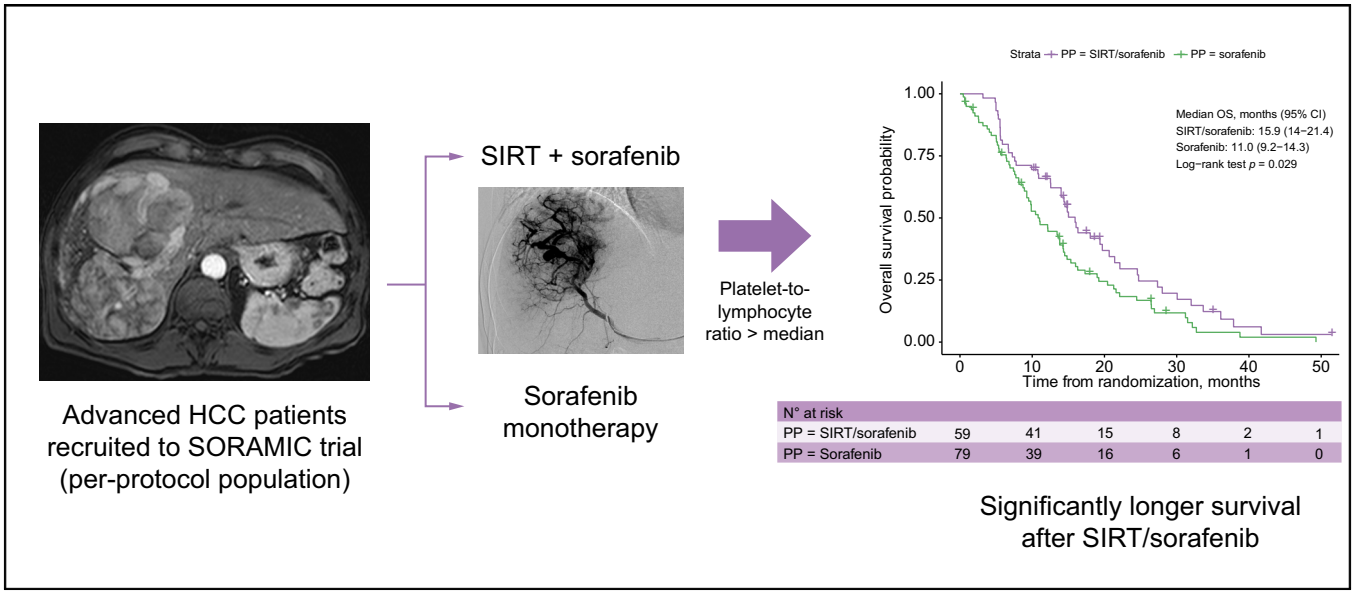
Graphical abstract



Highlights

- Platelet-to-lymphocyte ratio is a predictive factor in patients with advanced HCC.
- SIRT/sorafenib conferred a significant survival benefit *vs.* sorafenib monotherapy in patients with a high platelet-to-lymphocyte ratio.
- In patients with a low platelet-to-lymphocyte ratio, there is no significant difference in overall survival between treatment arms.

Impact and implications

Systemic therapies are the mainstay of treatment in patients with hepatocellular carcinoma at advanced stages. However, not all patients respond well to these treatments. In our analysis, using blood test parameters showing systemic inflammation status, we were able to identify patients who would benefit more from combined treatment with a locoregional treatment of radioembolization (or selective internal radiation therapy).

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Short communication

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Predictive value of platelet-to-lymphocyte and neutrophil-to-lymphocyte ratio in HCC treated with sorafenib and radioembolization

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Background & Aims: Herein we used data derived from the SORAMIC trial to explore the predictive value of systemic inflammatory markers (neutrophil-to-lymphocyte ratio [NLR] and platelet-to-lymphocyte ratio [PLR]) in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib monotherapy or the combination of selective internal radiation therapy (SIRT)/sorafenib.

Methods: Patients randomized to sorafenib monotherapy or SIRT/sorafenib within the per-protocol population of the SORAMIC trial were evaluated in this exploratory *post hoc* analysis. The median baseline values of NLR and PLR were used as cut-off values to describe subgroups. Kaplan-Meier curves with log-rank tests were used to evaluate median survival in the sorafenib and SIRT/sorafenib arms in each subgroup. Multivariable Cox regression analysis was applied to eliminate the effect of confounding factors.

Results: A total of 275 patients with a median overall survival of 12.4 months were included in this analysis. The median NLR value of the cohort was 2.77 and the median PLR was 26.5. There was no significant difference in overall survival between the sorafenib and SIRT/sorafenib arms in patients with low NLR (p = 0.72) and PLR (p = 0.35) values. In patients with high NLR values, there was no statistically significant difference in median overall survival between SIRT/sorafenib and sorafenib cohorts (12.1 *vs.* 9.2 months, p = 0.21). In patients with high PLR values, overall survival in the SIRT/sorafenib arm was significantly longer than in the sorafenib arm (15.9 *vs.* 11.0 months, p = 0.029). This significant difference was preserved in the multivariable analysis (SIRT/sorafenib arm: hazard ratio 0.65, 95% CI 0.44-0.96, p = 0.03) incorporating age, Child-Pugh grade, and alpha-fetoprotein levels.

Conclusions: PLR is a potential predictive factor of benefit from additional SIRT in patients with HCC receiving sorafenib therapy. The potential predictive value of PLR should be further evaluated in future trials.

Impact and implications: Systemic therapies are the mainstay of treatment in patients with hepatocellular carcinoma at advanced stages. However, not all patients respond well to these treatments. In our analysis, using blood test parameters showing systemic inflammation status, we were able to identify patients who would benefit more from combined treatment with a locoregional treatment of radioembolization (or selective internal radiation therapy).

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, and in most patients, HCC develops on the background of chronic inflammation of the liver.[1] Although the underlying etiology of liver disease differs in Asian and Western populations,[2] chronic inflammation leads to hepatocyte damage, accumulation of reactive oxygen species, genomic alterations, and eventually hepatocarcinogenesis.[3]

Systemic treatment with immune checkpoint inhibitors is the primary option in advanced HCC cases.[4,5] However, several other systemic treatments are also available, and second-line and further treatment options require further evidence. Sorafenib, a multitarget tyrosine kinase inhibitor, is currently a second-line treatment option in patients with HCC who progress after immune checkpoint inhibitor therapy or it can be used first-line when these treatments are unavailable or contraindicated.[6] Although its role in HCC treatment moved from patients with advanced stages to earlier stages in recent years, selective internal radiation therapy (SIRT) has been proposed as an alternative treatment option for patients with HCC with liver dominant disease who are not candidates for curative treatments

Keywords: Hepatocellular carcinoma; Sorafenib; Radioembolization; Platelet-to-lymphocyte ratio.

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or cannot tolerate systemic therapies.[6,7] Further evidence is needed for treatment selection especially in advanced HCC.

The systemic inflammatory response has been shown to be associated with the prognosis of various tumors.[8] Platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are the most commonly used systemic inflammatory markers. Several studies have evaluated the prognostic value of these markers in patients with HCC at various stages, and higher PLR and NLR values have been shown to be negative prognostic factors.[9–11] However, most of these studies were retrospective single-arm studies without a comparative treatment, and the predictive value of these markers in the setting of advanced HCC is yet to be defined.

In the randomized-controlled SORAMIC trial, the addition of SIRT failed to improve survival compared to sorafenib monotherapy.[12] This exploratory *post hoc* analysis of the per-protocol population of the palliative arm of the SORAMIC trial aimed to explore the predictive value of NLR and PLR in patients with advanced HCC receiving sorafenib monotherapy or the combination of SIRT and sorafenib.

Patients and methods

Study population

SORAfenib in combination with local MICro-therapy guided by gadolinium-EOB-DTPA-enhanced MRI (SORAMIC, EudraCT 2009-012576-27, NCT01126645) is a prospective, phase II, randomized-controlled study in patients with HCC that included three therapeutic study arms. The study protocol was approved by the competent authorities as well as the institutional review board, and all patients gave written informed consent. The inclusion and exclusion criteria for the SORAMIC trial have been described previously.[12] In summary, adult patients aged up to 85 years with a diagnosis of HCC in the intermediate stage (BCLC B) or advanced stage (BCLC C), preserved liver function (Child-Pugh scores A to B7), and an ECOG PS (Eastern Cooperative Oncology Group performance status) ≤2 were eligible. Extrahepatic metastasis was allowed if the disease was liver dominant and the lungs were not involved.

A total of 424 patients were recruited to the SORAMIC trial (intention-to-treat [ITT] population). 47.2% of the patients who were randomized to the SIRT/sorafenib arm and 16.3% of the patients randomized to the sorafenib arm did not receive allocated treatment as prescribed by the study protocol. Of the 288 patients randomized within the per-protocol population of the SORAMIC trial, 13 patients were excluded from this analysis due to missing lymphocyte (n = 12) or neutrophil (n = 1) counts at the time of randomization. The baseline characteristics of the study population are listed in Table 1.

In the palliative arm of the study, patients with HCC were randomized to sorafenib treatment either alone or combined with SIRT. Patients were randomized in an 11:10 ratio to receive either SIRT/sorafenib or sorafenib monotherapy. After randomization, patients in the sorafenib arm were started on treatment at a dose of 200 mg twice daily. The dose was escalated to 400 mg twice daily after 1 week. Treatment was continued until tumor progression or the emergence of a drug-related adverse event requiring discontinuation. Patients underwent SIRT in a lobar fashion using the semi-empiric BSA method for dosimetry. In patients with bilobar disease, the second treatment was performed 4–6 weeks after treating the disease-dominant liver lobe. Sorafenib treatment was initiated 3 days after the last SIRT session.

Statistical analysis

All statistical analyses were performed using R statistical and computing software, version 3.5.0 (http://www.r-project.org). Categorical variables were reported as counts and percentages, and continuous variables as means and standard deviations. The median values of NLR and PLR were used to define subgroups. The Kaplan-Meier method was used for estimates of overall survival, and 1- and 2-year survival rates. The log-rank test was used to compare survival groups. Cox regression models were used to assess the effects of cofounding factors on overall survival. The interaction effect of PLR and NLR with treatment were evaluated alone and adjusted with each other. Variables with a p value of <0.1 in the univariable analyses were analyzed in multivariable Cox regression models to explore prognostic factors of overall survival.

Results

In the ITT population, baseline NLR and PLR values were available for 397 patients. When the ITT population was grouped according to the median PLR (18.5) and NLR (2.84) values, there was no difference in OS between SIRT/sorafenib and sorafenib arms in patients with higher PLR values (12.5 *vs.* 11 months, p = 0.65) and with higher NLR values (9.9 *vs.* 8.7 months, p = 0.68). Similarly, no significant survival difference was observed in patients with lower PLR values (12 *vs.* 13.4 months, p = 0.44) and with lower NLR values (15.0 *vs.* 14.2 months, p = 0.91).

In the per-protocol population, 106 patients were randomized to the SIRT/sorafenib arm, 169 patients to the sorafenib monotherapy arm (baseline characteristics are given in Table 1). By the end of the study, 234 (85.1%) patients had died, and the median overall survival was 12.4 months. As in the main trial (SORAMIC), there was no significant difference in overall survival between the two treatment arms (13.3 *vs.* 11.3 months, p = 0.33).

Table 1. Baseline characteristics.

	Number	%
All cohort	275	100
Sex (male)	240	87
Age (>65)	161	59
Cirrhosis	216	80
Portal vein invasion (yes)	125	45
HCC etiology		
Hepatitis B	4	8.5
Hepatitis C	9	19.1
Alcohol	23	48.9
ECOG PS		
0	188	68
1	84	31
Unknown	3	1
Child-Pugh		
A	254	92
B	21	8
BCLC stage		
A&B	82	30
C	192	70
Extrahepatic metastasis	60	22

ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma.

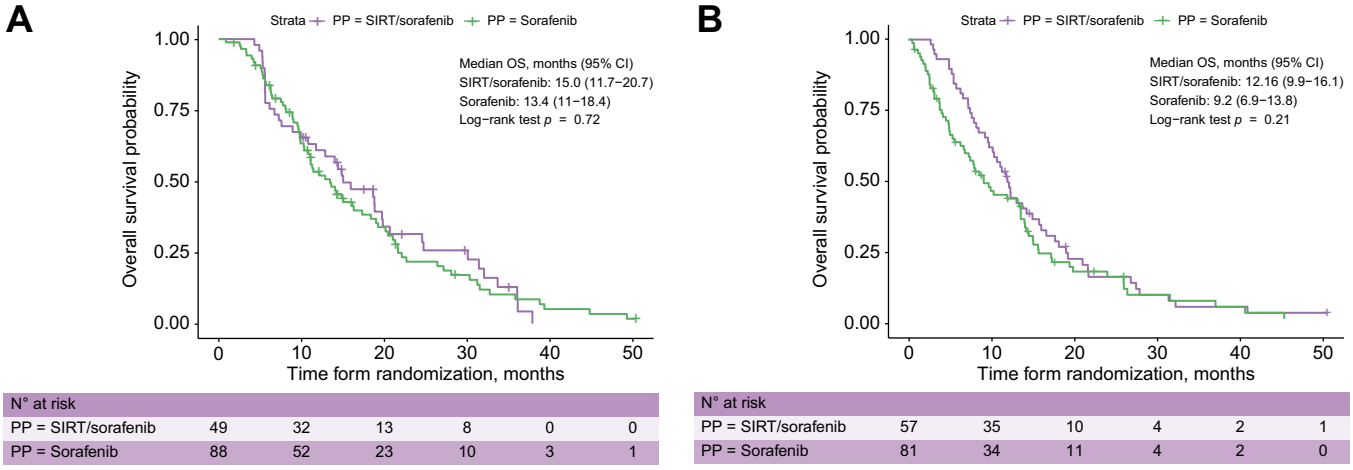
The median PLR at baseline of the cohort was 26.5 (range, 1.6-457.1), and the median NLR was 2.77 (range, 0.05-41.6). PLR was a significant prognostic factor in the SIRT/sorafenib arm (p = 0.029) but not in the sorafenib arm (p = 0.382) or the overall cohort (p = 0.495). Also, while NLR was a significant prognostic factor in the overall cohort (p = 0.011) and sorafenib arm (p = 0.018), it was not significant in the SIRT/sorafenib arm (p = 0.15).

When the cohort was divided into two subgroups using the median value of NLR, no significant difference was observed between SIRT/sorafenib and sorafenib cohorts in patients with NLR lower than 2.77 (15 *vs.* 13.4 months; hazard ratio [HR] 0.93, 95% CI, 0.63-1.4, p = 0.72; Fig. 1A). In patients with high NLR values, there was no statistically significant difference in the median overall survival between the SIRT/sorafenib cohort and the sorafenib cohort (12.1 *vs.* 9.2 months; HR 0.79, 95% CI 0.55-1.1, p = 0.21; Fig. 1B).

In patients with PLR lower than the median value, there was no significant difference in overall survival between SIRT/sorafenib and sorafenib cohorts (11.3 *vs.* 12.9 months; HR 1.2, 95% CI 0.82-1.8, p = 0.35). However, in patients with a PLR higher than the median value, the SIRT/sorafenib cohort had significantly longer overall survival than the sorafenib cohort (15.9 [14-21.4] *vs.* 11 [9.2-14.3] months; HR 0.66, 95% CI 0.46-0.96, p = 0.029; Fig. 2). The survival rates at 1 and 2 years were 66% (95% CI 55-79%) *vs.* 47% (95% CI 37-60%) and 30% (95% CI 19-46%) *vs.* 18% (95% CI 11-30%).

The interaction tests between inflammatory markers on overall survival showed a statistically significant interaction for PLR (p = 0.028), but not for NLR (p = 0.58). Similarly, PLR showed a significant interaction after adjustment for NLR (p = 0.035), but the interaction test was negative for NLR after adjustment for PLR (p = 0.56).

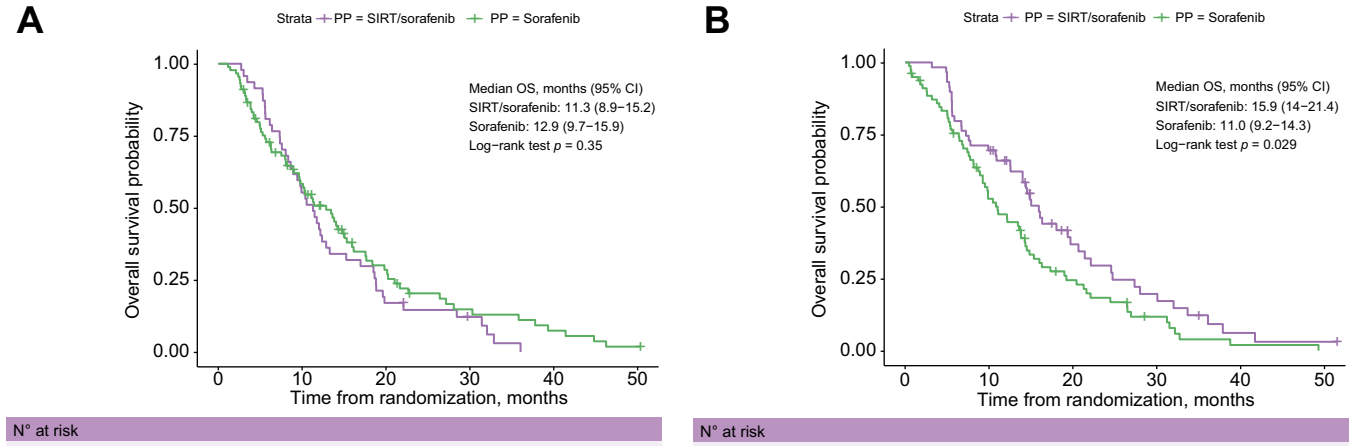
In order to eliminate confounding variables, other clinical parameters were analyzed in patients with a PLR higher than the cut-off using univariable Cox regression analysis. Besides the treatment arm, age (>65 years; HR 0.72, 95% CI 0.49-1.1, p = 0.088), Child-Pugh grade (HR 2.4, 95% CI 1.3-4.3, p = 0.006), and alpha-fetoprotein (>400 mg/dl; HR 0.77, 95% CI 0.52-1.2, p = 0.076) had a p value of <0.1 (Table 2). In the multivariable analysis (Fig. 3), the SIRT/sorafenib arm (HR, 0., 95% CI, 0.44-0.96, p =



N° at risk						
PP = SIRT/sorafenib	49	32	13	8	0	0
PP = Sorafenib	88	52	23	10	3	1

N° at risk						
PP = SIRT/sorafenib	57	35	10	4	2	1
PP = Sorafenib	81	34	11	4	2	0

Fig. 1. Kaplan-Meier curve showing overall survival of patients with NLR lower than 2.77 and higher than 2.77. (A) NLR lower than 2.77 and (B) NLR higher than 2.77 (p = 0.72 and p = 0.21, log-rank test). NLR, neutrophil-to-lymphocyte ratio.



N° at risk						
PP = SIRT/sorafenib	47	26	8	4	0	0
PP = Sorafenib	90	47	18	8	4	1

N° at risk						
PP = SIRT/sorafenib	59	41	15	8	2	1
PP = Sorafenib	79	39	16	6	1	0

Fig. 2. Kaplan-Meier curve showing overall survival of patients with PLR lower than 26.5 and PLR higher than 26.5. (A) PLR lower than 26.5 and (B) PLR higher than 26.5 (p = 0.35 and p = 0.029, log-rank test). PLR, platelet-to-lymphocyte ratio.

Table 2. Univariable and multivariable analysis of factors associated with overall survival in patients with high platelet-to-lymphocyte ratio.

Parameter	Univariable Cox regression analysis	
	HR (95% CI)	*p* value
Treatment arm (SIRT/Sorafenib)	0.66 (0.46-0.96)	**0.03**
Sex (male *vs.* female)	0.88 (0.49-1.6)	0.69
Age (≥65 *vs.* <65 years)	0.72 (0.49-1.1)	0.088
ECOG PS (1 *vs.* 0)	1.1 (0.77-1.7)	0.5
Cirrhosis	1.2 (0.79-2)	0.35
Portal vein invasion (yes *vs.* no)	0.94 (0.65-1.4)	0.74
Child-Pugh (B *vs.* A)	2.4 (1.3-4.3)	**0.0062**
Alcohol etiology (yes *vs.* no)	1.1 (0.78-1.6)	0.53
Hep B History (yes *vs.* no)	1.4 (0.71-2.8)	0.33
Hep C History (yes *vs.* no)	1.1 (0.66-1.7)	0.79
Extrahepatic metastasis	1.3 (0.86- 2.1)	0.2
AFP (<400 *vs.* ≥400 ng/ml)	0.71 (0.48-1)	0.076
BCLC stage (B *vs.* C)	0.93 (0.63-1.4)	0.72

Bold type indicates statistical significance.
AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

0.03) was significantly associated with overall survival, as well as Child-Pugh grade B (HR 2.05, 95% CI 1.05-4, $p = 0.036$).

Discussion

In this *post hoc* analysis of the SORAMIC trial, PLR was a significant predictive factor for benefit from combination treatment with SIRT in patients with HCC receiving sorafenib treatment.

Systemic inflammatory markers (NLR and PLR) are well-known prognostic factors associated with poor survival in various cancer types.[8,11] In patients with HCC treated with surgical resection, liver transplantation, locoregional therapies, SIRT, sorafenib, or immune checkpoint inhibitors, these markers have been shown to correlate with worse prognosis.[9–11,13,14] However, due to the lack of a control arm in these studies, the predictive value of NLR and PLR could not be evaluated. A prognostic factor is a marker that correlates with the course of the disease independent of the therapy; however, a predictive factor indicates a specific subgroup with a high likelihood of benefiting from a particular treatment. Thus, the evaluation of predictive factors is usually done in *post hoc* analyses of randomized-controlled trials. The predictive value of NLR has been evaluated in the combined analysis of SHARP and Asia-Pacific trials.[15] This analysis identified a significant benefit from sorafenib treatment in patients with HCC with low NLR (median overall survival, 426 *vs.* 302 days). However, in patients with high NLR values, the median overall survival of patients treated with sorafenib or placebo was similar (173 *vs.* 152 days; HR 0.84, 95% CI 0.66-1.05). These results indicate treatment resistance to tyrosine kinase inhibitors in patients with higher levels of inflammation. Similarly, in patients with advanced-stage HCC treated with ramucirumab, treatment benefit was observed in patients with low NLR, while no response was observed in patients with high NLR.[16] To date, according to our knowledge, the predictive value of PLR in patients with HCC has not been evaluated.

Unlike NLR, PLR is also correlated with the liver function of the patient. By incorporating the platelet count into the ALBI (albumin-bilirubin) score, the PALBI score has recently been described to account for the effect of portal hypertension. The PALBI score has been shown to be a prognostic factor in different stages of HCC[17] and superior to the ALBI score in terms of prognosis prediction.[18] Within recent years, several systemic agents have been proven to be effective in patients with advanced HCC.[4,19,20] Although immune checkpoint inhibitors are the first-line treatment, the sequence of second-line treatments is still being determined.[6]

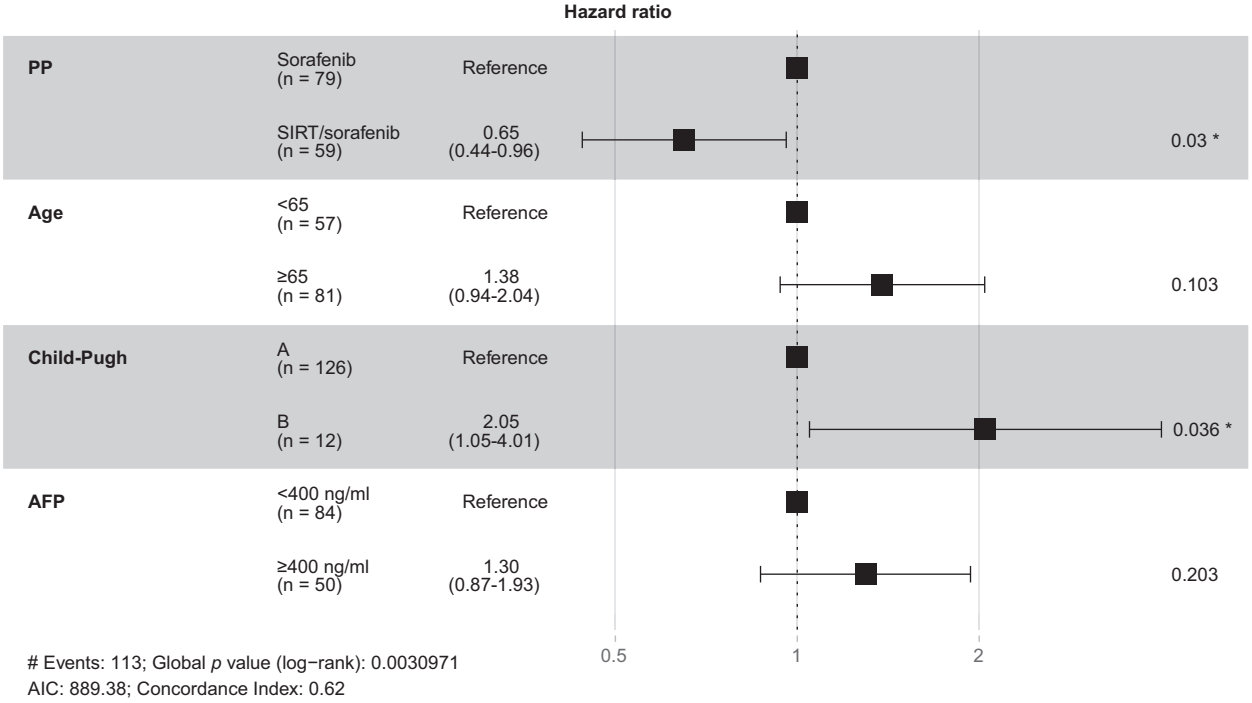


Fig. 3. Multivariable model of overall survival in patients with PLR higher than 26.5 (multivariable Cox regression analysis). SIRT/sorafenib arm ($p = 0.03$) and Child-Pugh grade B ($p = 0.036$) were significantly associated with overall survival. PLR, platelet-to-lymphocyte ratio; SIRT, selective internal radiation therapy.

Tyrosine kinase inhibitors are accepted as the second-line treatment in patients who progressed after immune checkpoint inhibitors. Also, they are still used first-line in patients with contraindications to immune checkpoint inhibitors. Several trials to assess second or further line treatments are ongoing or in the planning stage. Our study shows the benefit of using inflammatory-based markers in patient stratification. Furthermore, when there is no clear evidence for treatment selection in clinical decision-making, we suggest that combination treatments should be advocated in patients with higher PLR values.

Our study has some limitations. First, this was a *post hoc* analysis which resulted in a relatively limited sample size in some subgroups. That might be the reason behind the lack of statistical significance in the NLR high subgroup. Second, this study only evaluated patients in the per-protocol population. Similar to other trials on SIRT, there was considerable crossover, mainly from the SIRT/sorafenib arm, of patients who were not able to receive the allocated treatment. In addition to this, some patients did not receive sorafenib treatment after SIRT sessions. This situation is probably the reason for the missing survival difference between subgroups in the ITT population. Although focusing on the per-protocol population brings a potential limitation of excluding rapid progressor patients in the SIRT/sorafenib arm, survival analysis showed a statistically significant difference between treatment arms at 1 and 2 years in patients with high PLR values. Third, described cut-off values have not been externally validated and differ from previously reported cut-off values for NLR and PLR. However, the slight difference results from the inclusion of patients with relatively preserved liver function (Child-Pugh up to B7) in the trial, unlike the reported retrospective studies. Also, owing to the inclusion criteria and low number of patients in some subgroups, some known prognostic factors were not statistically significant in our analysis. Besides, liver function was evaluated in terms of Child-Pugh grade, and laboratory parameters were not assessed separately. Probably owing to dilution attributable to their predictive value, PLR and NLR were not significant prognostic factors in all treatment groups. Nevertheless, our study is the first to prove the predictive value of PLR in patients receiving sorafenib treatment for advanced HCC in a Western cohort from a multicenter randomized trial.

In conclusion, systemic inflammatory markers, especially PLR, may be used to identify patients who would benefit from combination treatments. Further analyses on the potential role of PLR as a predictive factor are warranted in further prospective trials, especially when tyrosine kinase inhibitors are being evaluated.

Abbreviations

HCC, hepatocellular carcinoma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SIRT, selective internal radiation therapy.

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Conflict of interest

Osman Öcal: Honoraria: Bayer. Max Seidensticker: Personal fees: Bayer, Sirtex. Najib Ben Khaled: Travel expenses: EISAI. Lecture honoraria: Falk Foundation and Astra Zeneca. Maciej Pech: Grants: Sirtex, Bayer; Personal fees: Sirtex. Bruno Sangro: Consultancy fees: Adaptimmune, Astra Zeneca, Bayer, BMS, Boston Scientific, BTG, Eisai, Eli Lilly, H3 Biomedicine, Ipsen, Novartis, Merck, Roche, Sirtex Medical and Terumo. Speaker fees: Astra Zeneca, Bayer, BMS, BTG, Eli Lilly, Ipsen, Novartis, Merck, Roche, Sirtex Medical and Terumo. Grants (to Institution): BMS and Sirtex Medical. Jens Ricke: Grants: Sirtex, Bayer; Personal fees: Sirtex, Bayer. Moritz Wildgruber: Speaker fees: Sirtex.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Osman Öcal, Max Seidensticker, Jens Ricke, Moritz Wildgruber: Conception and design of the study; Generation, collection, assembly, analysis and/or interpretation of data; Drafting or revision of the manuscript; Approval of the final version of the manuscript. Melanie A. Kimm, Thi Phuong Thao Hoang, Maciej Pech, Elif Öcal, Najib Ben Khaled, Bruno Sangro: Generation, collection, assembly, analysis and/or interpretation of data; Drafting or revision of the manuscript; Approval of the final version of the manuscript.

Data availability statement

The data that support the findings of this study are not publicly available but are available from the corresponding author on reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100995.

References

[1] El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142:1264–1273.e1261. https://doi.org/10.1053/j.gastro.2011.12.061.

[2] De Toni EN, Schlesinger-Raab A, Fuchs M, et al. Age independent survival benefit for patients with hepatocellular carcinoma (HCC) without metastases at diagnosis: a population-based study. Gut 2020;69:168–176. https://doi.org/10.1136/gutjnl-2018-318193.

[3] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301–1314. https://doi.org/10.1016/s0140-6736(18)30010-2.

[4] Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894–1905. https://doi.org/10.1056/NEJMoa1915745.

[5] Rimassa L, Finn RS, Sangro B. Combination immunotherapy for hepatocellular carcinoma. J Hepatol 2023;79:506–515. https://doi.org/10.1016/j.jhep.2023.03.003.

[6] Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76:681–693. https://doi.org/10.1016/j.jhep.2021.11.018.

[7] Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol 2017;18:1624–1636. https://doi.org/10.1016/s1470-2045(17)30683-6.

[8] Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 2014;106:dju124.

[9] Schobert IT, Savic LJ, Chapiro J, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as predictors of tumor response in hepatocellular carcinoma after DEB-TACE. Eur Radiol 2020;30:5663–5673.

[10] Hu B, Yang X-R, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014;20:6212–6222.

[11] Motomura T, Shirabe K, Mano Y, et al. Neutrophil–lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. J Hepatol 2013;58:58–64.

[12] Ricke J, Klümpen HJ, Amthauer H, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. J Hepatol 2019;71:1164–1174. https://doi.org/10.1016/j.jhep.2019.08.006.

[13] Li X, Han Z, Cheng Z, et al. Clinical significance of preoperative platelet-to-lymphocyte ratio in recurrent hepatocellular carcinoma after thermal ablation: a retrospective analysis. Int J Hyperthermia 2015;31:758–763.

[14] Pinato DJ, Stebbing J, Ishizuka M, et al. A novel and validated prognostic index in hepatocellular carcinoma: the inflammation based index (IBI). J Hepatol 2012;57:1013–1020.
[15] Bruix J, Cheng AL, Meinhardt G, et al. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. J Hepatol 2017;67:999–1008. https://doi.org/10.1016/j.jhep.2017.06.026.
[16] Llovet JM, Singal AG, Villanueva A, et al. Prognostic and predictive factors in patients with advanced HCC and elevated alpha-fetoprotein treated with ramucirumab in two randomized phase III trials. Clin Cancer Res 2022;28:2297–2305.
[17] Liu PH, Hsu CY, Hsia CY, et al. ALBI and PALBI grade predict survival for HCC across treatment modalities and BCLC stages in the MELD Era. J Gastroenterol Hepatol 2017;32:879–886. https://doi.org/10.1111/jgh.13608.
[18] Ho SY, Liu PH, Hsu CY, et al. Comparison of four albumin-based liver reserve models (ALBI/EZ-ALBI/PALBI/PAL) against MELD for patients with hepatocellular carcinoma undergoing transarterial chemoembolization. Cancers (Basel) 2023;15. https://doi.org/10.3390/cancers15071925.
[19] Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:282–296. https://doi.org/10.1016/s1470-2045(18)30937-9.
[20] Kudo M, Ikeda M, Motomura K, et al. A phase Ib study of lenvatinib (LEN) plus nivolumab (NIV) in patients (pts) with unresectable hepatocellular carcinoma (uHCC): study 117. J Clin Oncol 2020;38:513. https://doi.org/10.1200/JCO.2020.38.4_suppl.513. 513.