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The potential prognostic novel markers PIV and PILE score to predict survival outcomes at hepatocellular cancer

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Abstract. – OBJECTIVE: We aimed at investigating the prognostic significance of a novel immune marker, PIV and PILE score (a score composite from PIV, LDH and ECOG PS), in patients with HCC in a single center.

PATIENTS AND METHODS: 120 patients who met the criteria were included. PIV and PILE at the time of diagnosis were computed retrospectively. For PIV, the median value of 286.15 was taken as the cut-off. While <286.15 was considered low, ≥286.15 was considered high PIV. The PILE score included PIV (< median *vs.* ≥ median), lactate dehydrogenase level (<ULN vs. ≥ ULN) and ECOG-PS (0-1 vs. ≥ 2), with 0-1 points being low-risk PILE and 2-3 points being high-risk PILE group.

RESULTS: The median first-line PFS and OS in the low PIV group were 10 months (95% CI: 7.77-12.22) and 18 months (95% CI: 10.66-25.33), respectively. The PFS and OS in the high PIV group were 3 months (95% CI: 1.49-4.51) and 4 months (95% CI: 1.47-6.52), respectively (for PFS *p*=0.001, for OS *p*<0.001). In the low-risk (0-1) PILE score group, the median first line PFS and OS were 8 months (95% CI: 6.49-9.50) and 17 months (95% CI: 8.19-25.80), respectively. The high-risk (2-3) group, PFS and OS were 3 months (95% CI: 0-5.99), and 3 months (95% CI: 1.02-4.97), respectively (for PFS *p*=0.02, for OS *p*<0.001). In multivariate Cox regression analysis, PIV (HR: 1.81, 95% CI: 1.11-2.93, *p*=0.016) and ECOG PS (HR: 0.72, 95% CI: 1.34-3.19, *p*=0.01) were independent risk factors for OS.

CONCLUSIONS: The findings suggest that PIV and PILE score could be used as a prognostic biomarker at the time of diagnosis in patients with HCC. With prospective studies confirming these data, PIV and PILE can be used as a potential standard marker in HCC.

Key Words:
Pan-immune inflammation value, PILE Score, Hepatocellular carcinoma, Overall survival.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer worldwide and the third leading cause of cancer-related deaths[1]. Most HCC patients are diagnosed at moderate-to-advanced stages, and as such they cannot be cured[2]. Various invasive treatments (e.g., liver resection, liver transplantation, radiofrequency ablation (RF), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE) that provide a chance of cure in liver-limited diseases are emphasized. However, immunotherapy (IO) and anti-VEGF (Vascular Endothelial Growth Factor)-based treatments have now become standard in advanced and metastatic patients[3,4]. Despite many advances in treatment approaches, long-term overall survival (OS) outcomes in HCC patients are not yet satisfactory. In addition, non-invasive markers that predict survival in these patients are gaining more and more significance.

In recent years, many studies[5-7] suggest that inflammation-based blood parameters predict survival in patients with HCC. The role of systemic inflammatory response in tumor progression and metastasis are well-documented[8]. The host immune response against malignancy is a critical tool; it leads to systemic inflammation associated with altered blood markers due to overexpression of pro-inflammatory cytokines and signal-

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ing molecules[9]. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR) are the biomarkers often used in clinical practice to reveal systemic inflammation. High NLR, PLR, and MLR values are associated with tumor aggressiveness and poor prognosis[5,7]. In contrast to neutrophils, monocytes, and platelets, lymphocytes prevent tumor cells, and high blood lymphocyte levels are related to better OS[10,11].

Currently, a novel composite biomarker, pan-immune inflammation value (PIV), has been developed to demonstrate the inflammation status in malignancies. PIV encompasses blood neutrophils, monocytes, platelets, and lymphocyte values. It has been shown that PIV is prognostic in patients with colorectal, skin, lung, and breast cancer[12-15]. The PILE score is a potential new scoring system combining PIV with Eastern Cooperative Oncology Group Performance Status (ECOG PS) and blood lactate dehydrogenase (LDH) levels. The PILE score was shown to be prognostic on survival outcomes in treated cancer patients[16].

To our knowledge, no data in the literature relates to the prognostic and predictive use of PIV and PILE scores in patients with HCC. Hence, this study aimed at investigating the prognostic significance of PIV, PILE score, and NLR, PLR, and MLR for survival outcomes in HCC.

Patients and Methods

Patients

This retrospective study reviewed the data of 145 HCC patients, who were followed in our oncology center between 2013 and 2021. The study included 120 patients who met inclusion criteria. The study excluded patients with secondary malignancies and under 18 years of age, patients with comorbidities and conditions that might impact systemic inflammatory markers, such as active infection and steroid use, and those with missing data. In addition to demographic data of all patients, complete baseline blood counts and biochemistry parameters at the time of HCC diagnosis, viral markers (hepatitis B and C), and ECOG PS were recorded.

Systemic Inflammation Parameters

The PIV was calculated with this equation: [neutrophil count (10^3/mL) × platelet count (10^3/mL) × monocyte count (10^3/mL)] and lymphocyte count (10^3/mL)[12]. The median value was considered as the cut-off value for PIV. NLR, PLR, and MLR were calculated with the following formula: neutrophil count (10^3/mL)/lymphocyte count (10^3/mL), platelet count (10^3/mL)/lymphocyte count (10^3/mL), and monocyte count (10^3/mL)/lymphocyte count (10^3/mL). For NLR, PLR, and MLR, median values were considered cut-off levels. They were divided in two groups, with values above the median high and values below the median low.

PILE Score

The PILE score was generated using PIV, LDH, and ECOG PS. All three parameters were scored as 0 or 1 (PIV < median = 0 and ≥ median = 1, for LDH levels < ULN = 0 and ≥ ULN = 1, ECOG < 2 = 0 and ECOG ≥ 2 = 1). The total PILE score was calculated by summing the parameters from 0 to 3. Patients were divided in two groups: low-risk (0-1 points) and high-risk (2-3 points) for PILE scores[16,17].

Statistical Analysis

Statistical analyses were conducted with SPSS 25.0 software (IBM Corp., Armonk, NY, USA). The Mann-Whitney U test compared nonparametric data, while the Student's *t*-test compared parametric data. Chi-square or Fisher's exact test was used to compare categorical data. The Kaplan-Meier method was used for survival analysis, and the log-rank test for intergroup comparisons. Predictive factors impacting OS were determined by multivariate analysis with the Cox proportional hazards model, in which $p<0.05$ was considered statistically significant. OS was considered to be the primary endpoint.

Results

101 patients (84.2%) were male. The median age at diagnosis was 64 (IQR: 55-72). 29 patients (24.2%) diagnosed with HCC did not receive any treatment. Of the 91 patients who could be treated on the first line, 13.3% were resected, while 42.4% received local ablative therapies and 19.2% sorafenib. One patient underwent transplantation. There were 83 hepatitis B and 8 hepatitis C patients in our series. All hepatitis C patients received antiviral therapy. 74.2% (n=62) of hepatitis B patients received antiviral treatment. Only five patients (6.02%) had HBV DNA above 2,000 IU/ml. Patient characteristics and data on treatment are summarized in Table I.

Table I. Baseline characteristics and treatment data.

	All patients n = 120	(%)
Age-years, median (IQR)	64 (55-72)	
Gender		
Male	101	(84.2)
Female	19	(15.8)
Viral Hepatitis Status		
None	29	(24.2)
Hepatitis B	83	(69.2)
Hepatitis C	8	(6.7)
Cirrhosis		
Yes	88	(73.3)
No	32	(26.7)
Stage		
Limited Disease	59	(49.2)
Extraheaptic Disease	61	(50.8)
Number of Masses in Liver		
1	41	(34.2)
2-3	32	(26.7)
≥4	47	(39.1)
Performance Status		
ECOG 0-1	85	(70.8)
ECOG 2-4	35	(29.2)
First Line Therapies		
None	29	(24.2)
Sorafenib	40	(33.3)
Resection	23	(19.2)
RF	16	(13.3)
TARE	10	(8.3)
Transplantation	1	(0.8)
Second Line Therapies		
None	99	(82.5)
Sorafenib	20	(16.7)
Regorafenib	1	(0.8)
Third Line Therapies		
None	116	(96.6)
Regorafenib	4	(3.4)
PIV		
Low	60	(50)
High	60	(50)

ECOG = Eastern Cooperative Oncology Group, TACE = Transarterial Chemoembolization, TARE = Transarterial Radioembolization, PIV = Pan-Immune-Inflammation Value, IQR = Inter-quartile Range.

The median follow-up duration was 9.5 (IQR: 3-23) months. The progression-free survival (PFS) of patients who could be treated with first-line therapy was 7 months (95% CI: 5.19-8.80). The median OS was 9 months (95% CI: 5.93-12.06). On the other hand, the median OS was 17 months (95% CI: 12.40-21.59) for patients with liver-limited disease and 5 months in those with extrahepatic spread (95% CI: 2.91-7.05) (p = 0.001). The median OS was 14 months (95% CI: 8.77-19.22) in those with an ECOG PS of 0-1 and 2 months in those with an ECOG PS of 2-4 (95% CI: 0.55-3.44) (p = 0.001). Median OS was 13 months (95% CI: 6.55-1944) in 64 patients with serum LDH levels ≤ ULN and 6 months in 56 patients with serum LDH levels ≥ ULN (95% CI: 3.25-8.74) (p = 0.002).

Patients were divided in two groups, low and high PIV, based on the median PIV (286.15). Median first line PFS and OS in the low PIV group (< 286.15) were 10 months (95% CI: 7.77-12.22) and 18 months (95% CI: 10.66-25.33), respectively. In the high PIV group (≥ 286.15), PFS and OS were 3 months (95% CI: 1.49-4.51) and 4 months (95% CI: 1.47-6.52), respectively (for PFS p = 0.001, for OS p < 0.001).

In the low-risk (0-1) PILE score group, the median first line PFS and OS were 8 months (95% CI: 6.49-9.50) and 17 months (95% CI: 8.19-25.80), respectively. On the other hand, in the high-risk (2-3) group, PFS and OS were 3 months (95% CI: 0-5.99) and 3 months (95% CI: 1.02-4.97), respectively (for PFS p = 0.02, for OS p < 0.001).

Median cut-off values for NLR, PLR, and MLR were 3.02, 133.21, and 0.344, respectively. In all three parameters, patients with values above the cut-off had poorer first-line PFS and OS values than those with values below the cut-off (NLR: for PFS p = 0.048 for OS p < 0.001, PLR: for PFS p < 0.001 for OS p < 0.001, MLR: for PFS p = 0.03 for OS p = 0.001). Table II presents a summary of survival outcomes.

In the multivariate Cox regression analysis, high PIV (HR: 1.81, 95% CI: 1.11-2.93, p = 0.016) and ECOG PS ≥ 2 (HR: 0.72, 95% CI: 1.34-3.19, p = 0.01) were independent risk factors for OS (Table III).

Discussion

In our study, we found that PIV at diagnosis is an independent prognostic factor in HCC patients. Patients with high PIV had poorer PFS and OS outcomes. Moreover, our findings show that PILE, which includes PIV, ECOG PS, and LDH levels, also predict PFS and OS.

It has been determined that inflammation plays both key and complex roles in tumor growth, invasion, and metastasis[18]. HCC is one of the cancers that is the prototype for inflammation-associated cancer development. Chronic inflammation and fibrosis due to viral hepatitis, excessive alcohol intake, fatty liver disease, and cirrhosis play a role in the etiology of more

Table II. Survival outcomes.

	First Line PFS			OS		
	Month	95% CI	*p*-value	Month	95% CI	*p*-value
All patients	7	5.19-8.80		9	5.93-12.06	
Stage			< 0.001			0.001
Limited	10	5.47-14.52		17	12.40-21.59	
Extrahepatic	4	2.71-5.28		5	2.91-7.05	
ECOG			0.003			0.001
0-1	8	6.55-9.44		14	8.77-19.22	
2-4	2	0-4.13		2	0.55-3.44	
LDH			0.031			0.002
Normal	8	5.38-10.61		13	6.55-19.44	
≥ ULN	5	2.71-7.28		6	3.25-8.74	
PIV			0.001			< 0.001
Low	10	7.77-12.22		18	10.66-25.33	
High	3	1.49-4.51		4	1.47-6.52	
PILE			0.02			< 0.001
Low	8	6.49-9.50		17	8.19-25.80	
High	3	0-5.99		3	1.02-4.97	
NLR			0.048			< 0.001
Low	9	7.29-10.70		17	8.83-25.16	
High	4	2.53-5.46		4	0.96-7.03	
PLR			< 0.001			< 0.001
Low	9	7.03-10.96		17	5.14-28.85	
High	4	2.77-5.12		4	1.47-6.53	
MLR			0.03			0.001
Low	10	7.56-12.43		15	8.36-21.63	
High	4	2.80-5.19		4	1.15-.6.84	

PFS = Progression-Free Survival, OS = Overall Survival, NLR = Neutrophil to Lymphocyte Ratio, PLR = Platelet to Lymphocyte Ratio, MLR = Monocyte to Lymphocyte Ratio, ECOG = Eastern Cooperative Oncology Group, LDH = Lactat Dehydrogenase, PIV = Pan-Immune-Inflammation Value, PILE = Score derived from PIV, lactate dehydrogenase and Eastern Cooperative Oncology Group Performance Status, ULN = Upper Limits of Normal CI = Confidence Interval.

than 90% of HCC cases[19,20]. Many blood cells and proteins, markers of inflammation, play varying roles in the inflammation-cancer pathway. Neutrophils and platelets are associated with tumor growth, invasion, and progression, while lymphocytes indicate anti-tumor activity, especially in the tumor microenvironment[5,6,16]. It was demonstrated that monocytes contribute to the development of carcinogenesis through other complex pathways. Notably, tumor-associated macrophages (TAM) play the leading role. These cells were shown to contribute to

Table III. Multivariate analyses for overall survival.

	Hazard Ratio	95% CI	*p*-value
NLR (< 3.02 *vs.* ≥ 3.02)	1.078	0.689-1688	0.74
PLR (< 133.21 *vs.* ≥ 133.21)	1.632	0.980-2.719	0.06
MLR (< 0.344 *vs.* ≥ 0.344)	0.880	0.530-1.459	0.62
ECOG (0-1 *vs.* 2-4)	2.072	1.344-3.195	0.001
LDH (normal *vs.* ≥ ULN)	1.435	0.976-2.111	0.06
PIV (< 286.15 *vs.* ≥ 286.15)	1.813	1.119-2.938	0.01

NLR = Neutrophil to Lymphocyte Ratio, PLR = Platelet to Lymphocyte Ratio, MLR = Monocyte to Lymphocyte Ratio, ECOG = Eastern Cooperative Oncology Group, LDH = Lactat Dehydrogenase, PIV = Pan-Immune-Inflammation Value, CI = Confidence Interval.

angiogenesis, resulting in increased tumor cell proliferation and higher rates of distant metastases. Further, TAM has an immunosuppressive impact that increases tumor activity[21-23].

Various studies[6,7,24] have been used in inexpensive and easily accessible markers for HCC patients. A meta-analysis[24] found that NLR was a reliable and useful marker in predicting treatment response in HCC. In their own meta-analysis, Zhao et al[6] reported a correlation between high PLR and poorer survival rates, which is consistent with our study. Another study by Wang et al[7] determined that MLR predicted poor outcomes in patients receiving locoregional therapy, not only at baseline but at relapse. Consistent with these studies, ours found that high NLR, PLR, and MLR were associated with poorer survival outcomes.

Effective treatments and vaccines developed in recent years, as well as the rapid decline of viral forms, make non-alcoholic fatty liver disease (NAFLD) associated with HCC more often. In this pathology, where silent inflammation is at the forefront, it is important to recognize the development of cancer in the early stages and determine its prognosis[25]. Along with many new local and systemic treatments, imaging-based studies[26] can be effective in predicting treatment response. Despite these data, no markers have become standard in inflammation parameters with HCC. As markers used in literature typically have one or two components (e.g., neutrophil-lymphocyte, platelet-lymphocyte, monocytes, and lymphocyte), they fail to adequately reflect the inflammation-cancer relationship with different pathways and mechanisms. Studies[12] reveal that PIV, used initially in metastatic colorectal cancers, consisted of 4 blood components (neutrophil x platelet x monocytes/lymphocyte), and had a stronger prognosis than other inflammatory markers. Likewise, in our study, patients with high PIV had significantly poorer survival outcomes than those with low PIV. The effectiveness of PIV has been shown in different types of cancer. Fucà et al[13] conducted a study on patients with metastatic melanoma receiving first-line treatment. The authors reported that high PIV was associated with poorer OS and immunotherapy resistance. In different studies[14,27] on patients with ALK-positive NSCLC and on patients with breast cancer receiving neoadjuvant therapy, it was shown that PIV predicted pathological treatment response and survival outcomes.

The PILE score was previously used by Guven et al[16] to predict survival responses in cancer patients receiving IO. It is a novel, simple scoring system by scoring and summing each of the PIV, ECOG PS, and serum LDH levels. Another study[17] conducted on patients with SCLC demonstrated that high-risk PILE predicted poorer treatment response and survival outcomes. It is well-documented that ECOG PS is a crucial prognostic tool for HCC, as in many types of cancer[28]. Patients with a PS of 0-1 at the time of diagnosis have better treatment responses and survival outcomes[29]. LDH, a coenzyme, plays a vital role in anaerobic glycolysis. It is used as a potential or proven tumor marker in many cancers[30,31]. A meta-analysis[31] of 10 studies on HCC patients revealed that high LDH levels were associated with a poor prognosis.

Many scoring and staging systems were studied to predict local or systemic treatment responses, adverse effects, or survival outcomes in HCC. The Italian Liver Cancer Group (ITA.LI.CA) scoring system was found to be more effective in a meta-analysis investigating old and novel scoring systems (e.g., the albumin bilirubin (ALBI) grading system, a model to estimate survival in patients with the HCC (MESH) scoring system, Cancer of the Liver Italian Program (CLIP), Japanese Integrated Staging (JIS) scores, and Hong Kong Liver Cancer (HKLC) classification)[32]. Child-Pugh parameters, serum Alpha-Fetoprotein (AFP), disease burden, and functional status are frequently used in these systems[33]. Our study revealed that the simple potential PILE score, reflecting both laboratory and clinical-functional status, was associated with poorer PFS and OS outcomes in the high-risk group than in the low-risk group.

A correlation was shown between high HBV DNA levels and blood inflammatory parameters[34]. HBV DNA of 93.98% of hepatitis B patients was below 2,000 IU/ml. In addition, all hepatitis C patients received antiviral therapy and were HCV RNA negative in our series. Viral hepatitis did not have a major effect on blood inflammatory markers in our research.

Limitations

This study has some limitations: it was a retrospective and single-center study; therefore, despite impressive results, a prospective multicenter study can be more effective in evaluating PIV and PILE. There was also a risk of bias in some results due to the low number of patients and missing data.

Conclusions

This study demonstrated that PIV and PILE scores can be used as prognostic biomarkers at the time of diagnosis in HCC patients. To our knowledge, this was the first study investigating the prognostic value of PIV and PILE with HCC. Large prospective studies on this subject will provide better information, thereby reducing the possibility of bias.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

All participants in this study signed the informed consent.

Ethical Approval

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee from Health Sciences University, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (Decision No. 2022-03/1726).

Authors' Contribution

Conceptualization: I.K., S.K. Methodology: I.K, S.K., M.E.Y. Formal Analysis: I.K., S.K. Data Curation: S.K., M.E.Y. Writing-original Draft Preparation: I.K., S.K., O.B.C.O. Writing-review and editing: I.K., S.K., O.B.C.O. Supervision: All Authors.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the Hospital Information Management System and the corresponding author, upon reasonable request.

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