

# World Journal of *Gastrointestinal Oncology*

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- 1951 Identification of necroptosis-related lncRNAs for prognosis prediction and screening of potential drugs in patients with colorectal cancer

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- 1974 Long non-coding RNA CDKN2B-AS1 promotes hepatocellular carcinoma progression *via* E2F transcription factor 1/G protein subunit alpha Z axis

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Retrospective Study

## Baseline neutrophil-lymphocyte ratio and platelet-lymphocyte ratio appear predictive of immune treatment related toxicity in hepatocellular carcinoma

Sirish Dharmapuri, Umut Özbek, Hiren Jethra, Tomi Jun, Thomas U Marron, Anwaar Saeed, Yi-Hsiang Huang, Mahvish Muzaffar, Matthias Pinter, Lorenz Balcar, Claudia Fulgenzi, Suneetha Amara, Arndt Weinmann, Nicola Personeni, Bernhard Scheiner, Tiziana Pressiani, Musharraf Navaid, Bertram Bengsch, Sonal Paul, Uqba Khan, Dominik Bettinger, Naoshi Nishida, Yehia Ibrahim Mohamed, Arndt Vogel, Anuhya Gampa, James Korolewicz, Antonella Cammarota, Ahmed Kaseb, Peter R Galle, Anjana Pillai, Ying-Hong Wang, Alessio Cortellini, Masatoshi Kudo, Antonio D'Alessio, Lorenza Rimassa, David James Pinato, Celina Ang

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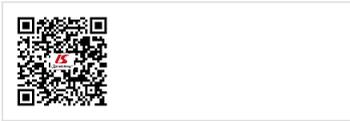
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## Abstract

### BACKGROUND

A well-recognized class effect of immune checkpoint inhibitors (ICI) is immune-related adverse events (IrAEs) ranging from low grade toxicities to life-threatening end organ damage requiring permanent discontinuation of ICI. Deaths are reported in < 5% of patients treated with ICI. There are, however, no reliable markers to predict the onset and severity of IrAEs. We tested the association between neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) at baseline with development of clinically significant IrAEs (grade  $\geq 2$ ) in hepatocellular carcinoma (HCC) patients treated with ICI.

### AIM

To test the association between NLR and PLR at baseline with development of clinically significant IrAEs (grade  $\geq 2$ ) in HCC patients treated with ICI.

### METHODS

Data was extracted from an international database from a consortium of 11 tertiary-care referral centers. NLR = absolute neutrophil count/absolute lymphocyte count (ALC) and PLR = platelet count/ALC. Cutoff of 5 was used for NLR and 300 for PLR based on literature. We also tested the association between

antibiotic and steroid exposure to IrAEs.

## RESULTS

Data was collected from 361 patients treated between 2016-2020 across the United States (67%), Asia (14%) and Europe (19%). Most patients received Nivolumab ( $n = 255$ , 71%). One hundred sixty-seven (46%) patients developed at least one IrAE, highest grade 1 in 80 (48%), grade  $\geq 2$  in 87 (52%) patients. In a univariable regression model PLR  $> 300$  was significantly associated with a lower incidence of grade  $\geq 2$  IrAEs (OR = 0.40;  $P = 0.044$ ). Similarly, a trend was observed between NLR  $> 5$  and lower incidence of grade  $\geq 2$  IrAEs (OR = 0.58;  $P = 0.097$ ). Multivariate analyses confirmed PLR  $> 300$  as an independent predictive marker of grade  $\geq 2$  IrAEs (OR = 0.26;  $P = 0.011$ ), in addition to treatment with programmed cell death ligand 1 (PD-1)/cytotoxic T lymphocyte-associated protein-4 (OR = 2.57;  $P = 0.037$ ) and PD-1/tyrosine kinase inhibitor (OR = 3.39;  $P = 0.01$ ) combinations. Antibiotic use was not associated with IrAE incidence (OR = 1.02;  $P = 0.954$ ). Patients treated with steroids had a  $> 2$ -fold higher incidence of grade  $\geq 2$  IrAEs (OR = 2.74;  $P < 0.001$ ), although 74% were prescribed steroids for the treatment of IrAEs.

## CONCLUSION

Given that high baseline NLR and PLR are associated with a decreased incidence of IrAEs, lower baseline NLR and PLR may be predictive biomarkers for the appearance of IrAEs in HCC treated with ICI. This finding is in keeping with several studies in solid tumors that have shown that baseline NLR and PLR appear predictive of IrAEs.

**Key Words:** Neutrophil-lymphocyte ratio; Platelet-lymphocyte ratio; Inflammatory biomarkers; Immunotherapy; Immune toxicity

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**Core Tip:** In this study of hepatocellular carcinoma (HCC) patients treated with immune checkpoint inhibitors (ICI), the association between two biomarkers, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), and immune-related adverse events (IrAEs) was examined. Data from 361 patients showed that a higher PLR ( $> 300$ ) was significantly associated with a lower incidence of grade  $\geq 2$  IrAEs. A trend was observed between a higher NLR ( $> 5$ ) and lower incidence of grade  $\geq 2$  IrAEs. Multivariate analyses confirmed PLR as an independent predictive marker for grade  $\geq 2$  IrAEs. These findings suggest that NLR and PLR could be potential predictive markers for IrAEs in HCC patients receiving ICI treatment.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) arises in a precancerous milieu of chronic inflammation heralded by oncoviral infection, alcohol consumption or steatohepatitis in up to 90% of patients[1-3]. Systemic inflammatory response driven by pro-inflammatory cytokines such as vascular endothelial growth factor (VEGF), matrix metalloproteinases and interleukin-18 plays a pivotal role in oncogenesis as well as tumor progression and metastasis[3-5].

Immune checkpoint inhibitors (ICI) and their combinations can induce robust and durable anti-tumor responses in a subset of patients with advanced Hepatocellular Carcinoma (aHCC). The IMbrave-150 and HIMALAYA trials both showed significantly improved progression free and overall survival with ICI combinations compared to sorafenib, making atezolizumab/bevacizumab and durvalumab/tremelimumab standard front-line options[6]. ICI monotherapies such as nivolumab and pembrolizumab remain an integral part of the treatment paradigm owing to their safety, tolerability and improved quality of life over tyrosine kinase inhibitors[6-9]. With the advent of ICI as the mainstay of treatment of aHCC, considerable interest has been generated towards studying the relationship between inflammation and its impact on outcomes of patients treated with ICIs.

A well-recognized class effect of these drugs is immune treatment-related adverse events (IrAEs) ranging from low grade toxicities managed supportively with or without steroids or other immunosuppressive agents to potentially life-threatening end organ damage requiring hospitalization and permanent discontinuation of ICI. Treatment related deaths are reported in less than 5% of patients treated with ICIs [Yervoy® (ipilimumab) prescribing information. Bristol-Myers

Squibb Company. Princeton, NJ, United States (2013)[10-12]. At present, there are no reliable markers to predict the onset and severity of IrAEs. This study was undertaken with the objective of examining the relationship between inflammatory ratios such as neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) with the incidence of IrAEs in aHCC patients treated with ICIs. In addition, given recent data demonstrating that steroids can modulate NLR[13] and that antibiotics may increase the risk of IrAEs[14,15], we also aimed to explore the interaction between these drugs, NLR, PLR and IrAEs.

## MATERIALS AND METHODS

### Patients

Data was extracted from a large international database from a consortium of 11 tertiary-care referral centers located in the United States, Europe and Asia. To be eligible patients had to have: (1) A diagnosis of HCC made by histopathology or imaging criteria according to international guidelines; (2) be candidate for ICI monotherapy or combinations for HCC; (3) not amenable to curative or loco-regional therapy following local multidisciplinary tumor board review, and (4) have measurable disease according to RECIST 1.1 criteria. Between June 2016 and September 2020, 427 patients were included in the database. In our final analysis we excluded 66 patients due to incomplete IrAE data (final  $n = 361$ ). Of the 361 patients included in the final analysis, 242 (67%) were treated in the United States, 51 (14%) in Asia and 68 (19%) in Europe. Institutional review board approval was obtained at Mount Sinai Hospital and in each participating institution. All study-related procedures and data collection were conducted in accordance with the Declaration of Helsinki and in accordance with good clinical practice.

### Methods

NLR was calculated as the ratio of absolute neutrophil count to absolute lymphocyte count (ALC), and PLR was calculated as the ratio of platelet count to ALC from blood draws at baseline. A cutoff of 5 was used for NLR groups and 300 for PLR based on literature[16-20]. Information regarding IrAEs was extracted by manual review of clinical documentation at each cycle and records of hospitalizations. Each IrAE was defined and documented per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 per the treating physician and validated by a member of the study group. Grade  $\geq 2$  IrAEs were considered clinically significant since these patients typically require close monitoring and/or initiation of corticosteroid therapy and/or permanent discontinuation of ICI, while grade 1 toxicities only require supportive measures.

Patients were considered exposed to corticosteroid if  $> 10$  mg of prednisone (or equivalent) was administered for  $> 24$  h within 30 d prior to or concomitantly until permanent cessation of immunotherapy. Similarly, patients were considered to have been exposed to antibiotic therapy if they were received within 30 d from starting ICI therapy and up to 30 d after cycle 1 of immunotherapy were based on literature which suggests early antibiotic exposure as a detrimental factor influencing ICI efficacy[21,22].

### Statistical analysis

Descriptive statistics were calculated to summarize baseline status, including demographics, disease characteristics, and treatment characteristics. Univariable logistic models were conducted to identify associations between adverse events, inflammatory scores and other baseline characteristics. Continuous variables were presented as medians and minimum-maximum values, and categorical variables as frequency and proportions. Clinically relevant variables such as baseline alpha-fetoprotein (AFP), barcelona clinic liver cancer stage, presence of cirrhosis, child-turcotte pugh class, eastern cooperative oncology group performance status, etiology of chronic liver disease, and use of corticosteroids and antibiotics for IrAE management were considered as predictors of toxicity and were analyzed by univariable and multivariable logistic regression models.  $P$  values of less than 0.05 were considered to indicate statistical significance. All analyses were performed using R statistical package version 4.0.3 (R Core Team 2020)[23].

## RESULTS

### Patient and disease characteristics

A total of 361 patients had documented IrAE data and were included in the final analysis, of whom 242 (67%) were treated in the United States, 51 (14%) in Asia and 68 (19%) in Europe (Figure 1). Table 1 shows the breakdown of key clinicopathologic characteristics in patients who had none or grade  $< 2$  and grade  $\geq 2$  IrAEs. A majority had underlying cirrhosis ( $n = 263$ , 73%). Two hundred and seventy-six (76%) patients had child-pugh class A and 74 (20%) had class B liver function. The most common etiologies were hepatitis C virus infection in 153 (42%) patients, followed by hepatitis B virus infection in 77 (21%). Most patients received programmed cell death ligand 1 (PD-1) monotherapy ( $n = 305$ , 84%; nivolumab = 255; pembrolizumab = 20), followed by combination PD-1/cytotoxic T lymphocyte-associated protein-4 (CTLA-4) ( $n = 28$ , 8%), PD-1/tyrosine kinase inhibitor (TKI) ( $n = 24$ , 7%) and others in 4 (1%).

### IrAEs

One hundred and sixty-seven (46%) patients were documented as having developed at least one IrAE, highest grade 1 in 80 (48%), grade 2 or higher in 87 (52%) patients. There was one treatment related death reported. The most common IrAE

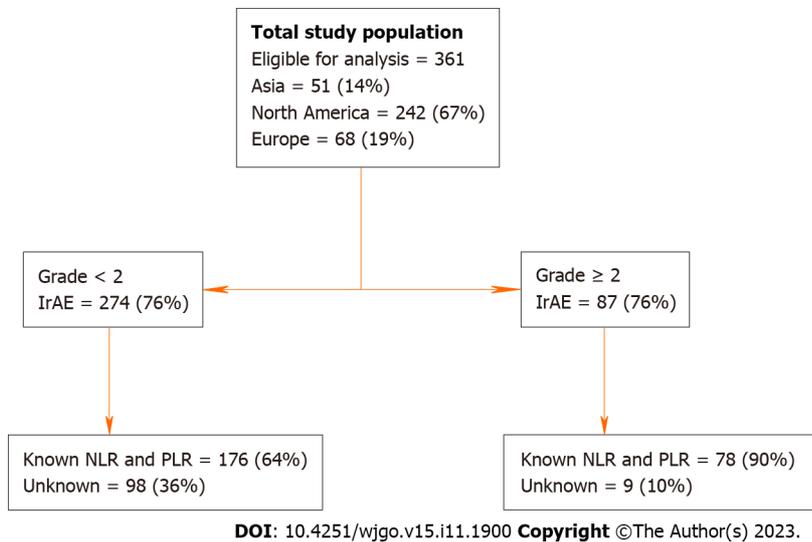
**Table 1** Baseline patient characteristics, *n* (%)

Variable	Category	No AEs or AEs grade < 2	AEs grade ≥ 2	OR	95%CI	P value
<i>n</i> = 361		274 (76) <sup>1</sup>	87 (24)			
Age (Median)		65	64	0.99	(0.97, 1.01)	0.450
Sex	Male	222 (61)	65 (18)	1.00		
	Female	52 (14)	22 (7)	1.44	(0.82, 2.56)	0.206
AFP (Median)		115	29	1.00	(1, 1)	0.850
Known cirrhosis	Yes	201 (56)	62 (17)	0.90	(0.53, 1.54)	0.702
	No	73 (20)	25 (7)	1.00		
Known PVT	Yes	61 (17)	18 (5)	0.60	(0.33, 1.1)	0.100
	No	124 (34)	61 (17)	1.00		
NLR	NLR ≤ 5	122 (34)	62 (17)	1.00		
	NLR > 5	54 (15)	16 (5)	0.58	(0.31, 1.1)	0.096
	Unknown	98 (27)	9 (2)			
PLR	PLR ≤ 300	145 (40)	72 (20)	1.00		
	PLR > 300	31 (9)	6 (2)	0.39	(0.16, 0.98)	0.044
	Unknown	98 (27)	9 (2)			
Child pugh class	A	202 (56)	74 (20)	1.00		
	B	61 (17)	13 (4)	0.58	(0.3, 1.12)	0.105
	C	7 (2)	0 (0)	0.00	(0, Inf)	0.986
	Unknown	4 (1)	0 (0)			
HCV	Yes	112 (31)	41 (11)	1.29	(0.79, 2.09)	0.305
	No	162 (45)	46 (13)	1.00		
HBV	Yes	59 (16)	18 (5)	0.95	(0.53, 1.72)	0.867
	No	215 (60)	69 (19)	1.00		
EtOH	Yes	48 (13)	17 (5)	1.14	(0.62, 2.11)	0.669
	No	226 (63)	70 (19)	1.00		
NASH	Yes	37 (10)	8 (2)	0.65	(0.29, 1.45)	0.292
	No	237 (66)	79 (22)	1.00		
BCLCs	A	9 (2)	1 (1)	1.00		
	B	66 (18)	25 (7)	3.41	(0.41, 28.31)	0.256
	C	194 (53)	61 (17)	2.83	(0.35, 22.79)	0.328
	D	4 (1)	0 (0)	0.00	(0, Inf)	0.985
	Unknown	1 (1)	0 (0)			
Extra Hepatic Disease	Yes	100 (28)	36 (10)	0.73	(0.43, 1.23)	0.239
	No	87 (24)	43 (12)	1.00		
	Unknown	87 (24)	8 (2)			
ECOG	0	168 (47)	77 (21)	1.00		
	1	18 (5)	2 (1)	0.24	(0.05, 1.07)	0.062
	Unknown	88 (24)	8 (2)			
Steroid use	Yes	57 (16)	37 (10)	2.74	(1.61, 4.64)	0.0002
	No	190 (53)	45 (12)			

Antibiotic use	Unknown	27 (7)	5 (2)	1.01	(0.52, 1.98)	0.95
	Yes	42 (12)	14 (4)			
	No	205 (56)	67 (19)			
Treatment	Unknown	27 (7)	6 (2)	3.00	(1.35, 6.67)	0.007
	PD-1	244 (68)	61 (17)			
	PD-1/CTLA-4	16 (4)	12 (3)			
	PD-1/TKI	12 (3)	12 (3)			
	PD-1/other	1 (0)	1 (0)			
	CTLA-4	1 (0)	1 (0)	4.00	(0.25, 64.86)	0.329
				4.00	(0.25, 64.86)	0.32

<sup>1</sup>Of 274 (76%) with no adverse events (AEs) or AEs grade < 2, 80 (22%) had grade 1 AEs and 194 (54%) had no AEs.

OR: Odds ratio; CI: Confidence Interval; AEs: Adverse events; AFP: Alpha-fetoprotein; ECOG: Eastern cooperative oncology group; BCLCs: Barcelona clinic liver cancers; NASH: Nonalcoholic steatohepatitis; HBV: Hepatitis B virus; HCV: Hepatitis C virus infection; PLR: Platelet-lymphocyte ratio; NLR: Neutrophil-lymphocyte ratio; PVT: Portal vein thrombosis; PD-1: Programmed cell death ligand 1; CTLA-4: Cytotoxic T-lymphocyte antigen-4; TKI: Tyrosine kinase inhibitor.



**Figure 1 Study flow chart.** IrAEs: Immune-related adverse events; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio.

was hepatitis (41%) followed by constitutional symptoms including fatigue, anorexia, chills (40%). **Table 2** details the IrAE incidence by groups and severity. No significant differences in age, sex, risk factors including Ethanol, hepatitis B and C, presence of cirrhosis, portal vein thrombosis and median AFP were noted between patients who developed IrAEs of grade  $\geq 2$  and those who did not.

Treatment with combinations PD-1/CTLA-4 and PD-1/TKI were associated with a 3 (OR = 3;  $P = 0.007$ ) and 4-fold (OR = 4;  $P = 0.001$ ) higher incidence of grade  $\geq 2$  IrAEs over PD-1 only. In a multivariable regression analysis, treatment with both PD-1/CTLA-4 (OR = 2.57;  $P = 0.037$ ) and PD-1/TKI (OR = 3.39;  $P = 0.01$ ) were independently associated with incidence of grade  $\geq 2$  IrAEs.

### Relationship between NLR, PLR and IrAEs

NLR was  $\leq 5$  in 184 (51%) patients and  $> 5$  in 70 (20%) patients. The proportion of patients with an NLR  $< 5$  or  $> 5$  did not differ significantly between the IrAE groups. PLR was  $\leq 300$  in 217 (60%) and  $> 300$  in 37 (11%) patients (**Table 1**). In a univariable regression model, baseline PLR  $> 300$  was significantly associated with a lower incidence of grade  $\geq 2$  IrAEs (OR = 0.40;  $P = 0.044$ ). Similarly, NLR  $> 5$  was associated with a trend toward lower incidence of grade  $\geq 2$  IrAEs (OR = 0.58;  $P = 0.097$ ). The multivariable regression analysis showed an independent association between PLR  $> 300$  (OR = 0.26;  $P = 0.011$ ) with a lower incidence of grade 2 or higher IrAEs (**Table 3**).

### Impact of concomitant medications on NLR, PLR and IrAEs

A total of 94 patients received corticosteroids, including 47 patients who developed an IrAE. Steroid use was associated with a greater than 2-fold higher incidence of grade  $\geq 2$  IrAEs (OR = 2.74;  $P < 0.001$ ) and maintained a significant association in a multivariable regression analysis (OR = 4.43;  $P < 0.001$ ). Notably, the indication for steroids in 35 (74%) of

**Table 2 Immune-related adverse events incidence by groups<sup>1</sup>, n (%)**

IrAE by organ system n = 167	Grade < 2	Grade ≥ 2
Dermatological	43 (26)	15 (9)
Colitis	19 (11)	10 (6)
Hepatitis	40 (24)	29 (17)
Endocrine	18 (11)	11 (7)
Polyarthritits	3 (1)	1 (0)
Pneumonitis	10 (6)	9 (5)
Constitutional	52 (31)	15 (9)
Other	15 (9)	22 (13)

<sup>1</sup>The incidence of immune-related adverse events (IrAEs) has been presented by patient groups categorized as those with IrAEs of grade < 2 and those with IrAEs of grade ≥ 2, stratified by the affected organ systems. IrAE: Immune-related adverse events.

**Table 3 Univariable and multivariable models to predict grade 2 or higher adverse events**

	Odds ratio	95%CI	P value
Univariable model:			
PLR (> 300)	0.40	(0.16, 0.98)	0.044
NLR (> 5)	0.58	(0.31, 1.10)	0.097
Steroid use	2.74	(1.62, 4.64)	< 0.001
Antibiotics use	1.02	(0.52, 1.98)	0.954
Treatment			
PD-1 CLTA-4	3	(1.35, 6.67)	0.007
PD-1 TKI	4	(1.71, 9.34)	0.001
Other <sup>1</sup>	4	(0.55, 28.97)	0.170
Multivariable model:			
PLR (> 300)	0.26	(0.09, 0.74)	0.011
Steroid use	4.43	(2.21, 8.88)	< 0.001
Treatment			
PD-1/CLTA-4	2.57	(1.06, 6.24)	0.037
PD-1/TKI	3.39	(1.34, 8.56)	0.01
Other <sup>1</sup>	3.50	(0.21, 57.86)	0.381

<sup>1</sup>Other include single agent cytotoxic t-lymphocyte antigen-4 and other immune checkpoint inhibitors/tyrosine kinase inhibitor combinations. CI: Confidence interval; PLR: Platelet-lymphocyte ratio; NLR: Neutrophil-lymphocyte ratio; PD-1: Programmed cell death ligand 1; CLTA-4: Cytotoxic t-lymphocyte antigen-4; TKI: Tyrosine kinase inhibitor.

the 47 patients who developed an IrAE, was for the treatment of IrAEs.

Fifty-six patients received antibiotics for treatment of an infection or as pre-transarterial chemoembolisation prophylaxis. Twenty-nine of these patients had documented IrAEs. Antibiotics use was not associated with IrAE incidence (OR = 1.02; P = 0.954) (Table 3).

NLR and PLR did not differ significantly between patients who did and did not receive steroids [(NLR; HR = 1.03; P = 0.69) (PLR; HR = 1.04; P = 0.53)] or antibiotics [(NLR; HR = 1.13; P = 0.35) (PLR; HR = 1.21; P = 0.10)].

## DISCUSSION

ICIs induce a diverse array of toxicities, presenting as single organ inflammatory disease such as hepatitis to multi system

toxicity[24]. Most IrAEs present within the first few months of therapy, though they can manifest throughout the course of treatment[25,26]. They most frequently affect barrier tissues such as the skin (-20%)[26], gastrointestinal tract (-50%)[27] and the respiratory epithelium (-35%), followed by endocrine organs (6%-12%)[28] and less frequently cause joint inflammation (-10%), neurological, cardiovascular or hematologic toxicity (1%-5%). Treatment related deaths are also reported in < 5% of patients treated with ICI[24,25].

Currently, there are no prospectively validated biomarkers to predict the onset or the severity of IrAEs though several have been studied such as preexisting autoimmune disease, body-mass index, and gut microbiome among others[29,30]. Onset of IrAEs however, closely correlates with clinical benefit from ICI therapy based on several reports across disease types[31-38], including from our consortium[39]. Conversely, inflammatory ratios such as NLR and PLR have consistently demonstrated an inverse relationship with response and survival outcomes from ICI therapy[40,41]. Considering the correlation between these inflammatory ratios and IrAEs, as well as the broad accessibility, ease of execution, and rapidity of these tests, it is pertinent to study the relationship between these inflammatory ratios and IrAEs.

Our study demonstrates, for the first time, a potential inverse association between baseline PLR and NLR with incidence of clinically significant (*i.e.*, grade  $\geq 2$ ) IrAEs in aHCC treated with ICI, particularly for PLR which was an independent predictive marker of grade  $\geq 2$  IrAEs. Such an association has also been described in other diseases, particularly in non-small cell lung cancer[42-44]. While the individual relationships between NLR, PLR, IrAE incidence and ICI response directionally align with the existing literature, the mechanisms linking the systemic inflammatory response and the development of IrAEs require further study.

An elevated NLR in a chronic inflammatory state such as cancer, has been shown to be associated with an increased concentration of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) in the peripheral blood[45] as well as tumor-infiltrating neutrophils[43]. The role of PMN-MDSCs in immune tolerance by means of upregulated expression of arginase-1, increased production of reactive oxygen species, Nitrous Oxide, prostaglandin E2 among others is well described in literature[46]. It may therefore be reasonable to hypothesize that the suppression of the anti-tumor T lymphocyte responses in the tumor microenvironment heralded by PMN-MDSCs likely contributes to the poor clinical outcomes and a lower incidence of IrAEs. Additionally, Lymphocytes are an integral components in the immune response against tumors, and an elevated presence of tumor-infiltrating lymphocytes within the neoplastic tissue holds prognostic value, correlating with improved survival outcomes[47]. Patients with higher NLR and PLR have a state of relative lymphopenia, signifying an impaired immune response. This likely accounts for both a reduced incidence of IrAEs as well as poorer prognostic outcomes on ICI.

The mechanistic rationale for the predictive nature of PLR is less well understood, though may be partly explained by the hypercortisolemic state of chronic inflammatory disease[48]. Hypercortisolemia results in elevated platelet counts, heightened platelet activation, and concurrently lowers lymphocyte counts[49-51]. Thrombocytosis has been demonstrated to exert pro-tumor effects, facilitating tumor progression and metastasis through the production of VEGF and platelet-derived growth factor production. These factors subsequently recruit neutrophils and monocytes, a phenomenon that ultimately culminates in adverse prognostic outcomes[40,52]. Beyond their role in hemostasis, platelets modulate the immune response *via* both pro and anti-inflammatory mechanisms. Platelets have been shown to express functional CD154, a molecule critical for primary and memory T cell responses[53]. In addition to acting as antigen presenting cells[54], platelets also augment CD8 T cell responses *via* CD154 mediated secondary signaling[55]. Their anti-inflammatory effect is exerted *via* platelet-derived cytokine TGF  $\beta$  which inhibits FoxP3(-) T-cells, among other mechanisms[56]. The vast role of platelets in immune modulation remains underrepresented in literature.

Consistent with published literature[24,57], our study shows a 2 to 3-fold higher incidence of grade  $\geq 2$  IrAEs in patients receiving ICI combinations over monotherapy. In the HIMALAYA trial, the incidence of any grade toxicity was 76% in the combination arm, as opposed to 52% in the durvalumab only arm[58]. Similarly, combination Atezolizumab-bevacizumab led to any grade toxicity rate of 98% in the IMbrave-150 study[6]. Understanding how to balance the toxicity of ICI and its combinations, while maximizing its anti-tumor activity remains a critical unmet need and may hinge on identifying early predictors of impending toxicity.

Our study also demonstrates that the use of steroids was strongly associated with a 2-fold increase in the incidence of grade  $> 2$  IrAEs. However, of the 47 patients with IrAEs who received steroids, 74% were prescribed them for treatment of IrAEs. Thus, the association is likely explained by steroids being used to treat IrAEs and does not indicate a causal relationship. Due to the small number of patients treated with steroids, a distinct analysis of the impact of steroid exposure before ICI therapy *vs* its use in the management of IrAEs is not feasible.

Antibiotic exposure has been shown to impair efficacy of ICI and increase the risk of IrAEs by inducing loss of gut microbial diversity and dysbiosis[59,60]. Our study showed no association between antibiotic exposures and IrAE risk. Another study published from this consortium also showed an improved progression free survival in patients with early antibiotic exposure while on ICI therapy[21], contrasting with studies in other solid tumors. HCC is associated with an immunosuppressive microbiome in the setting of underlying cirrhosis, which may explain the differential effect of antibiotics compared to other solid tumors[21]. We also noted no significant differences in NLR and PLR between patients who did and did not receive steroids and antibiotics.

We understand the limitations of our study include its retrospective design, a relatively small sample size and lack of correlative studies. Our non-prospective design precludes definitive conclusions regarding the predictive value of NLR and PLR but can be considered hypothesis-generating and warrants further validation in larger, prospective cohorts. Despite the fact that most patients in our study were treated with ICI monotherapy, which contrasts with the current standard of care of atezolizumab-bevacizumab, the findings remain significant as ICIs are a crucial component of the treatment paradigm for HCC. Data were collected and entered manually; some missing IrAE data were noted in our analyses. History regarding other chronic inflammatory conditions that could affect NLR and PLR were not collected

during chart review and therefore cannot be evaluated. The influence of other confounding factors such as thrombocytopenia from chronic liver disease on NLR and PLR remains a subject of investigation to be explored in a larger prospective cohort. The documentation of IrAEs was based on the NCI-CTCAE v5.0 per the treating physician and validated by a member of the study group, however inconsistencies may exist due to the subjective nature of some groups of IrAEs.

In conclusion, our study demonstrates an interesting association between baseline inflammatory ratios and onset of IrAEs in a real-world cohort of HCC patients, although this conclusion warrants prospective validation. Given that high baseline NLR and PLR are associated with a lower incidence of clinically significant IrAEs, lower baseline NLR and PLR may be predictive biomarkers for the appearance of IrAEs in HCC treated with ICI. These findings have potentially important implications, as identifying and monitoring patients at high risk of developing IrAEs may help decrease mortality and morbidity associated with IrAE. Our findings also provide real world evidence for increased toxicity of ICI combinations over monotherapy in HCC.

## CONCLUSION

In conclusion, our study demonstrates an interesting association between baseline inflammatory ratios and onset of IrAEs in a real-world cohort of HCC patients, although this conclusion warrants prospective validation. Given that high baseline NLR and PLR are associated with a lower incidence of clinically significant IrAEs, lower baseline NLR and PLR may be predictive biomarkers for the appearance of IrAEs in HCC treated with ICI. These findings have potentially important implications, as identifying and monitoring patients at high risk of developing IrAEs may help decrease mortality and morbidity associated with IrAE. Our findings also provide real world evidence for increased toxicity of ICI combinations over monotherapy in HCC.

## ARTICLE HIGHLIGHTS

### Research background

Immune checkpoint inhibitors (ICI) are known to cause immune-related adverse events (IrAEs) ranging from mild to severe, sometimes leading to treatment discontinuation, with less than 5% of patients experiencing fatal outcomes. Nevertheless, there are currently no dependable markers to forecast the occurrence and seriousness of IrAEs.

### Research motivation

Nevertheless, there are currently no dependable markers to forecast the occurrence and seriousness of IrAEs.

### Research objectives

In this study, we examined whether baseline neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are linked to the development of clinically significant IrAEs (grade  $\geq 2$ ) in patients with hepatocellular carcinoma (HCC) undergoing ICI treatment.

### Research methods

Data was gathered from a global database comprising data from 11 specialized medical centers. NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count (ALC), while PLR was calculated as the platelet count divided by ALC, with predefined cutoff values of 5 for NLR and 300 for PLR as per existing literature. Additionally, we explored the connection between the use of antibiotics and steroids with the occurrence of IrAEs.

### Research results

Data was collected from 361 patients treated between 2016 and 2020 across the United States (67%), Asia (14%), and Europe (19%), with the majority receiving Nivolumab (71%). Of these patients, 46% experienced at least one IrAE, with 48% being grade 1 and 52% grade  $\geq 2$ . In a univariable regression analysis, a PLR  $> 300$  was significantly linked to a lower incidence of grade  $\geq 2$  IrAEs (OR = 0.40;  $P = 0.044$ ), while there was a trend towards lower incidence with NLR  $> 5$  (OR = 0.58;  $P = 0.097$ ). Multivariate analysis confirmed PLR  $> 300$  as an independent predictor of grade  $\geq 2$  IrAEs (OR = 0.26;  $P = 0.011$ ), along with treatment involving programmed cell death ligand 1 (PD-1)/cytotoxic T lymphocyte-associated protein-4 (OR = 2.57;  $P = 0.037$ ) and PD-1/tyrosine kinase inhibitor combinations (OR = 3.39;  $P = 0.01$ ). The use of antibiotics did not show a significant association with IrAE incidence (OR = 1.02;  $P = 0.954$ ), while patients treated with steroids had more than a twofold increased risk of grade  $\geq 2$  IrAEs (OR = 2.74;  $P < 0.001$ ), although a majority of them received steroids for IrAE treatment.

### Research conclusions

Considering that elevated baseline NLR and PLR are correlated with a reduced occurrence of IrAEs, lower baseline NLR and PLR levels could potentially serve as predictive biomarkers for the development of IrAEs in HCC patients undergoing ICI treatment.

**Research perspectives**

Considering that elevated baseline NLR and PLR are correlated with a reduced occurrence of IrAEs, lower baseline NLR and PLR levels could potentially serve as predictive biomarkers for the development of IrAEs in HCC patients undergoing ICI treatment.

**FOOTNOTES**

**Author contributions:** Dharmapuri S contributed to study concept and design, acquisition of data, analysis, and interpretation of data and drafting of the manuscript; Özbek U and Jethra H performed statistical analysis; Jun T, Marron TU, Saeed A, Huang YH, Muzaffar M, Pinter M, Balcar L, Fulgenzi C, Amara S, Weinmann A, Personeni N, Scheiner B, Pressiani T, Navaid M, Bengsch B, Paul S, Khan U, Bettinger D, Nishida N, Mohamed YI, Vogel A, Gampa A, Korolewicz J, Cammarota C, Kaseb A, Galle PR, Pillai A, Wang YH, Cortellini A, Kudo M, D'Alessio A and Rimassa L performed acquisition of data; Pinato DJ and Ang C contributed to study concept and design, analysis and interpretation of data, drafting of the manuscript, and study supervision; Both contributed equally and should be considered joint senior authors. All authors performed critical revision of the manuscript for important intellectual content.

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