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Development of a simple and objective prognostication model in patients with advanced solid malignant tumor treated with immune checkpoint inhibitors: A pan-cancer analysis

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Introduction

Immune checkpoint inhibitors (ICIs) have shown therapeutic efficacies against various types of malignant tumor. However, response patterns to ICIs are heterogeneous and only a minority of patients respond to ICIs; thus, the remaining patients are forced to be exposed to ineffective, toxic and costly treatments. It is necessary to identify reliable biomarkers to predict therapeutic outcomes in advanced cancer patients receiving ICIs.

To date, there have been a number of studies evaluating biomarkers, including tumor mutation burden, PD-L1 and tumor-infiltrating lymphocytes. However, assessments of these types of biomarkers accompany several problems, such as the availability of tumor tissues, intratumoral heterogeneity and high costs for these assays. Furthermore, the predictive performances of these biomarkers are still not enough to introduce them into routine clinical practice.

In this study, we performed a pan-cancer analysis of clinical data from patients with advanced solid malignant tumors who were treated with ICIs in order to identify factors associated with the prognosis, and to develop a reliable, easy and low-cost prognostication model.

Methods

This study is approved by the Institutional Review Board of Hamamatsu University School of Medicine (No. 21-288).

This study retrospectively included a total of 329 consecutive patients who were diagnosed with advanced solid malignant tumors and treated with ICIs between October, 2014 and June, 2021.

The clinicopathological data were obtained from medical records. Prior to the start of ICI therapy, laboratory data were measured by standard clinical testing methods. All statistical analyses were performed using EZR software (ver. 1.40), and p values <0.05 were considered significant. Cut-off value was determined according to the Youden index obtained from receiver operating characteristic (ROC) analysis.

Table 1. Patient characteristics

Parameter	n=329
Age (years) (median, range)	70 (24-89)
Sex (male) (n, %)	244 (74.2)
BMI (kg/m^2) (median, range)	20.5 (12.3-36.1)
Primary tumor (n, %)	
Lung	89 (27.1)
Kidney	70 (21.2)
Urinary tract	52 (15.8)
Skin	50 (15.2)
Stomach	30 (9.1)
Esophagus	21 (6.4)
Head and neck	17 (5.2)
Regimen (n, %)	
Nivolumab	155 (47.1)
Pembrolizumab	136 (41.3)
Atezolizumab	26 (7.9)
Ipilimumab+Nivolumab	7 (2.1)
Avelumab	3 (0.9)
Durvalumab	2 (0.6)
Number of previous systemic therapies (n, %)	
0	123 (37.4)
1	110 (33.4)
2	64 (19.5)
≥3	32 (9.7)

Results

Patient characteristics were shown in Table 1.

Median follow-up period in the 329 patients was 9.5 months. Complete and partial response achieved in 23 (7.0%) and 91 (27.7%), respectively, thus overall response rate was 34.7%. The median progression free survival and overall survival(OS) were 4.5 months and 17.3 months, respectively.

To identify predictive factors of OS after the start of ICI therapy, Cox's regression analyses conducted (Table 2). Low BMI, high CRP, low hemoglobin, low lymphocytes and high platelets were shown to have independent impacts by the multivariate analysis.

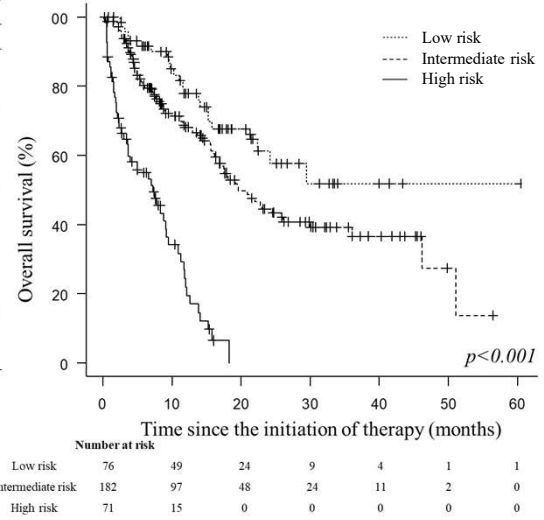
A prognostication model was developed by the independent factors. Patients were classified into the three groups according to the positive numbers of these 5 risk factors: favorable risk group with 0 or 1 risk factor (n=76, 23.1%); intermediate risk group with 2 or 3 risk factors (n=182, 55.3%); and poor risk group with 4 or 5 risk factors (n=71, 21.6%). The median OSs in the favorable, intermediate and poor risk groups were not reached (95% CI, 22.4 months-not reached), 19.5 months (95%CI, 16.3-26.0 months) and 7.2 months (95%CI, 3.6-9.2 months), and significant difference among these three groups was noted as shown in Figure.

Table 2. Univariate and multivariable analyses as predictors of overall survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (>70 years)	0.89	0.65 - 1.22	0.48			
Sex (Male)	0.88	0.62 - 1.23	0.45			
BMI (<20 kg/m^2)	**1.64**	**1.20 - 2.24**	**0.0021**	**1.45**	**1.05 - 2.01**	**0.025**
Albumin (<3.7 g/mL)	1.87	1.36 - 2.57	<0.001	1.04	0.72 - 1.51	0.84
LDH (>167 U/mL)	1.63	1.03 - 2.57	0.38			
CRP (>0.96 mg/dL)	**2.65**	**1.93 - 3.64**	**<0.001**	**1.80**	**1.24 - 2.64**	**0.0023**
Hemoglobin (<11.4 g/dL)	**2.01**	**1.46 - 2.75**	**<0.001**	**1.70**	**1.19 - 2.43**	**0.0037**
Neutrophils (>6156 10^2/μL)	2.74	1.88 - 3.99	<0.001	1.32	0.79 - 2.20	0.29
Lymphocytes (<1588 10^2/μL)	**2.29**	**1.47 - 3.57**	**<0.001**	**2.71**	**1.62 - 4.54**	**<0.001**
Platelets (>24.9 10^4/μL)	**1.81**	**1.32 - 2.48**	**<0.001**	**2.08**	**1.42 - 3.06**	**<0.001**
NLR (>6.8)	1.87	1.37 - 2.57	<0.001	1.66	1.00 - 2.76	0.052
PNR (>259)	2.23	1.62 - 3.08	<0.001	0.80	0.52 - 1.23	0.31

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; LDH, lactate dehydrogenase; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PNR, platelet-to neutrophil ratio

Figure. OS according to three risk groups



Discussions

Current researches for the identification of biomarkers for ICI therapies have tended to explore detailed characteristics of tumors by genetic and molecular biological approaches. However, it is usually difficult to introduce them into real-world clinical practice considering complicated procedure, high cost and insufficient reproducibility[1]. This study focused on simple and objective biomarkers that can be easily achievable and found that significantly favorable OS could be expected in patients with five factors described above. To date, there have been several studies reporting outcomes similar to those in this study. For example, Cortellini et al analyzed clinical outcomes of pan-cancer patients receiving ICIs, and found a significant association between high BMI and improved prognostic outcomes[2].

It is of interest to develop a useful system predicting prognosis based on the independent risk factors, there were significant differences in OSs among these groups. Although several prognostication systems for patients receiving ICI therapies have been reported[3,4], this might be an initial study showing the utility of such a system across multiple solid tumor types, consisting of only parameters easily achievable during routine clinical practice.

Limitations. Firstly, this was a retrospective study, including a comparatively small number of patients as a pan-cancer analysis. Secondly, cut-off point of each parameter was determined by ROC analysis; however, it is also preferable to assess optimal cut-off points.

1)Lei Y eti al. Front Oncol. 2021;11:617335 2)Cortellini A et al. J Immunother Cancer. 2019;7:57
3)Niu Z et al. Front Oncol. 2022;12: 852803 4)Zheng Y et al. BMC Cancer. 2021;21:1322

Conclusions

We developed a prognostic tool for advanced cancer patients treated with ICI therapy using five independent risk factors of the poor OS, including low BMI, high CRP, low hemoglobin, high neutrophils and low lymphocytes, which may properly stratify these patients into the favorable, intermediate or poor risk group. This model is a simple and objective system without non-numeric values unachievable by laboratory tests. Thus, this model represents a potential alternative to currently employed biomarkers for the risk classification of advanced solid cancer patients received ICI therapies.

COI I have no COI with regard to our presentation.

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