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

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Abstract

Background Systemic therapy using immune checkpoint inhibitors (ICIs) has recently become prevalent in the treatment of patients with various types of advanced cancers; however, difficulties are still associated with predicting the outcomes of patients receiving ICIs due to heterogenous responses to these agents. Therefore, the objective of the present study was to develop a prognostic model for advanced cancer patients treated with ICIs.

Patients and methods This study retrospectively analyzed the impact of clinical parameters on overall survival (OS) in 329 patients with several advanced solid malignant tumors who received systemic therapy using ICIs.

Results The primary tumors of 329 patients were as follows: lung (n=89), kidney (n=70), urinary tract (n=52), skin (n=50), stomach (n=30), esophagus (n=21), and head and neck (n=17). Median OS after the introduction of ICIs was 17.3 months. Among the factors that correlated with OS in a univariate analysis, body mass index, C-reactive protein, hemoglobin, lymphocytes, and platelets were identified as independent predictors of OS in a multivariate analysis. Following the classification of patients into 3 groups based on positive numbers of these independent risk factors, median OS was not reached in the favorable risk group with 0 or 1 risk factor (n=76), 19.5 months in the intermediate-risk group with 2 or 3 risk factors (n=182), and 8 months in the poor risk group (n=71) with 4 or 5 risk factors.

Conclusions Although this is a simple and objective model, it may be used as a reliable tool to predict the outcomes of advanced cancer patients receiving ICIs across multiple tumor types.

Statements and Declarations

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Author's Contribution

AK was involved in data collection, contributed to data interpretation and wrote the manuscript. YI, HK, Kensuke F, Kazuhito F, AI,YM and KT were involved in data collection.MK conceived the idea of the study.HM was involved in data collection and contributed to the interpretation of the results. All authors reviewed the manuscript draft and revised it critically on intellectual content. All authors approved the final version of the manuscript to be published.

Conflict of interest.

All authors declare that they have no conflicts of interest that might be relevant to the contents of this manuscript

1 Introduction

Cancer cells may induce immune tolerance by engaging inhibitory immune checkpoints, resulting in evasion from T-cell responses and, ultimately, the induction of tumor progression [1]. Based on this mechanism, immune checkpoint inhibitors (ICIs), including antibodies against programmed cell death 1 (PD-1), its ligand (PD-L1), and cytotoxic T lymphocyte antigen 4, were developed to stimulate cancer-specific immune responses, and have demonstrated therapeutic efficacy against various types of malignant tumors, such as melanoma, renal cell carcinoma, and non-small cell lung cancer [2]. However, response patterns to ICIs are extremely heterogeneous among different cancer types, and only a small proportion of advanced cancer patients generally respond to ICIs; therefore, the other patients are exposed to ineffective, toxic, and costly treatments with ICIs [3]. Therefore, the identification of reliable biomarkers to predict therapeutic outcomes in advanced cancer patients receiving ICIs is urgently needed.

To date, a number of studies have evaluated the usefulness of biomarkers for ICI therapy, including the tumor mutation burden, neoantigens, PD-L1, and tumor-infiltrating lymphocytes [4]. However, assessments of these types of biomarkers are associated with a number of issues, such as the availability of tumor tissues, intratumoral heterogeneity, and the high cost of these assays. Furthermore, although the predictive performance of these biomarkers was shown to be sufficient in some studies, evidence to support their introduction into routine clinical practice has been inadequate [5]. Therefore, we herein performed a pan-cancer analysis of clinical data from 329 patients with advanced solid malignant tumors who were treated with systemic therapy using ICIs in order to identify factors closely associated with the

prognosis of these patients and develop a reliable prognostication model after ICI therapy across multiple cancer types.

2 Methods

2.1 Study design and patients

The Research Ethics Committee of our institution approved the design of this study, and the need to obtain written informed consent for involvement from all of the patients included was waived due to its retrospective design.

This study retrospectively included 329 consecutive patients who were diagnosed with advanced solid malignant tumors, including lung (n=89), kidney (n=70), urinary tract (n=52), skin (n=50), stomach (n=30), esophagus (n=21), and head and neck (n=17) cancers, and were subsequently treated with ICIs at our institution between October, 2014 and June, 2021.

2.2 Treatment with ICIs

In this series, each patient was treated with ICIs by monotherapy using atezolizumab, avelumab, durvalumab, nivolumab, or pembrolizumab or combined therapy using ipilimumab plus nivolumab. As a rule, ICI therapy was performed based on a standard dosing schedule corresponding to each solid tumor type; however, dose modifications to each ICI therapy were permitted according to the severity of adverse events considering the product label. Treatment protocols for the administration of ICIs used in the present study underwent a regulatory review at our institution.

2.3 Evaluation

The clinicopathological data of each patient were obtained from medical records. Prior to the initiation of ICI therapy, laboratory data were measured by standard clinical testing methods, and all patients were subjected to radiological evaluations by computed tomography, fluoro-D-glucose positron emission tomography, a radionuclide bone scan, and/or gallium scintigraphy. In this study, progression-free survival (PFS) was defined as the duration from the initiation of treatment with ICIs to disease progression or the date of death from any cause, and overall survival (OS) as the duration between the initiation of treatment with ICIs to the date of death from any cause or censorship on the day of the last follow-up visit.

2.4 Statistical analysis

All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, ver. 1.40), and p values <0.05 were considered to be significant. OS and PFS rates were evaluated by the Kaplan-Meier method, and the Log-rank test was performed to evaluate differences among plural groups. The prognostic significance of certain parameters was assessed using uni- and multivariate Cox proportional hazards models. Cut-off values were selected according to the Youden index obtained from receiver operating characteristic (ROC) curves plotted for the value of each parameter to predict OS.

3 Results

3.1 Patient characteristics

Table 1 summarizes the clinicopathological characteristics of the 329 patients included in the present study. The primary solid tumors of these 329 patients were as

follows: lung (n=89), kidney (n=70), urinary tract (n=52), skin (n=50), stomach (n=30), esophagus (n=21), and head and neck (n=17). ICI therapies for these patients were as follows: nivolumab (n=155), pembrolizumab (n=136), atezolizumab (n=26), ipilimumab and nivolumab (n=7), avelumab (n=3), and durvalumab (n=2).

3.2 Patient outcomes

The median follow-up period for 329 patients was 9.5 months (interquartile range, 4.5-18.0 months). Complete and partial responses after treatment with ICIs were achieved by 23 (7.0%) and 91 (27.7%) patients, respectively; therefore, the objective response rate (ORR) in 329 patients was 34.7%. Median PFS after the introduction of ICIs in 329 patients was 4.5 months (95% confidence interval [CI], 3.7-5.5 months). During the follow-up period, death from any cause occurred in 160 patients (48.6%). Median OS from the initiation of ICI therapy was 17.3 months (95% CI, 15.2-21.3 months), and 1-, 3-, and 5-year OS rates were 62.0, 35.1, and 17.7%, respectively (Fig. 1).

The present study focused on simple and objective parameters, including age, sex, body mass index (BMI), and several serum markers, as potential prognostic indicators, and optimal cut-off values for these parameters were selected using ROC curves. Table 2 shows a comparison of OS between the two groups stratified according to these cut-off values, and significantly favorable OS was observed in patients with high BMI, high albumin, low lactate dehydrogenase (LDH), low C-reactive protein (CRP), high hemoglobin, low neutrophils, high lymphocytes, low platelets, a low neutrophil-to-lymphocyte ratio (NLR), and low platelet-to-lymphocyte ratio (PNR).

3.3 Predictors of OS

To identify predictive factors of OS after the start of ICI therapy in 329 patients, uni- and multivariate Cox regression analyses of several parameters were conducted (Table 3). Univariate analyses revealed that OS correlated with BMI, albumin, CRP, hemoglobin, neutrophils, lymphocytes, platelets, NLR, and PNR. Of these parameters, only BMI, CRP, hemoglobin, neutrophils, and lymphocytes were identified as independent predictors of OS in the multivariate analysis.

Based on these results, a novel prognostication model was subsequently developed by defining low BMI (<20 kg/m^2), high CRP (>0.96 mg/dL), low hemoglobin (<11.4 g/dL), high neutrophils (>6156×10^2/μL), and low lymphocytes (<1588×10^2/μL) as risk factors for poor OS. Included patients were classified into the following three groups according to positive numbers of these 5 risk factors: a favorable risk group with 0 or 1 risk factor (n=76, 23.1%); an intermediate risk group with 2 or 3 risk factors (n=182, 55.3%); and a poor risk group with 4 or 5 risk factors (n=71, 21.6%). As shown in Fig. 2, median OS 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 a significant difference in OS was observed among the three groups.

4 Discussion

The recent introduction of ICIs into routine clinical practice has revolutionized therapeutic strategies for the treatment of patients with various types of advanced malignant tumors [1,2]. However, despite significant improvements in patient

outcomes, the treatment of cancer patients with ICIs achieves low response rates due to the heterogeneous responses of advanced malignant tumors to this type of agent [3]. Collectively, these findings strongly suggest the urgent need for the development of biomarkers to predict the clinical course of advanced cancer patients treated with ICIs because the predictive performance of currently available biomarkers for ICI therapy is insufficient [4,5]. Therefore, we retrospectively assessed the outcomes of 329 patients with several advanced solid malignant tumors who received systemic therapy with ICIs at our institution in order to develop a reliable prognostication system for ICI therapy across multiple solid tumor types.

In this series, 6 different ICI therapies were performed for 329 patients with advanced solid tumors, including 7 different origins. The following oncological outcomes were achieved in these patients: ORR, 34.7%; median PFS, 4.5 months; and median OS, 17.3 months. Despite differences among tumor types, oncological outcomes in the present study were consistent with those in previous studies [6-10]. The CheckMate 057 trial targeting previously treated non-squamous non-small-cell lung cancer patients treated with nivolumab revealed that ORR, PFS, and OS were 19%, 2.3 months, and 12.2 months, respectively [6], while the outcomes of the KEYNOTE-426 trial for treatment-naïve renal cancer patients receiving pembrolizumab and axitinib were as follows: ORR, 59.3%; PFS, 15.1 months; and OS, not reached [7]. Accordingly, the advanced cancer patients included in the present study were assumed to be an optimal cohort for the assessment of a prognostication system.

Research to identify biomarkers for ICI therapies has generally investigated the detailed characteristics of tumors using genetic and molecular biological approaches

[4]; however, even if promising findings are achieved by these approaches, it is typically difficult to introduce them into real-world clinical practice due to a number of issues, such as the complexity of the procedure, high cost, and insufficient reproducibility [5]. Therefore, the present study focused on simple and objective biomarkers that may be easily achievable, including sex, BMI, and representative serum markers, and showed that significantly favorable OS may be expected in patients with high BMI, high albumin, low LDH, low CRP, high hemoglobin, low neutrophils, high NLR, and low PNR. To date, a number of studies have reported outcomes similar to those in the present study [11-15]. Cortellini et al. examined the clinical outcomes of pan-cancer patients receiving ICIs, and found that high BMI correlated with better outcomes [11], while Valero et al. showed significantly poor PFS and OS after ICI therapy in patients with higher NLR based on data from a pan-cancer analysis [13].

A system that predicts the outcomes of advanced cancer patients treated with ICIs needs to be developed. In the present study, uni- and multivariate analyses identified the following five factors as independent predictors of poor OS: low BMI, high CRP, low hemoglobin, high neutrophils, and low lymphocytes. Based on these results, when 329 patients were classified into 76, 182, and 71 who were positive for 0 or 1, 2 or 3, and 4 or 5 independent risk factors, respectively, significant differences were observed in OS among these groups. These results suggest that the consideration of these five risk factors will contribute to the development of a novel system that precisely predicts OS after treatment with ICIs. Although several prognostication systems for patients receiving ICI therapies have been reported [16-18], to the best of our knowledge, this is the first study to show the utility of such a

system across multiple solid tumor types that only consists of parameters that are easily achievable during routine clinical practice.

There are several limitations that need to be addressed. This was a retrospective analysis that included a small number of patients for a pan-cancer analysis; therefore, the results obtained need to be confirmed in a prospective study with a larger sample size. Furthermore, the cut-off point for each parameter was selected using ROC curves; however, it is also preferable to assess optimal cut-off points based on data from a larger number of patients. In addition, as described above, the prognostication system described in the present study resulted in an unbalanced distribution into three risk groups, characterized by a high proportion of patients corresponding to the intermediate risk group. In consideration of the clinical application of such a system, it may be attractive to equally distribute targeted patients into three risk groups. Moreover, although the advantage of the present prognostication system is its simplicity and objectivity, it will be interesting to simultaneously consider complex parameters, such as the expression of PD-L1 and the infiltration status of lymphocytes, and also to examine whether its predictive performance may be enhanced by these additional assessments.

5 Conclusion

We conducted a pan-cancer analysis of 329 patients with advanced solid malignant tumors who received systemic therapy using ICIs. ORR, PFS, and OS in these patients were 34.7%, 4.5 months, and 17.3 months, respectively. Furthermore, we developed a novel prognostic tool for advanced cancer patients treated with ICI therapy using five independent risk factors for poor OS: low BMI, high CRP, low

hemoglobin, high neutrophils, and low lymphocytes, which may properly stratify these patients into the favorable, intermediate, and poor risk groups. Collectively, these results suggest that despite the requirement for validation in a prospective setting, the present prognostication model is a simple and objective system without non-numeric values unachievable by laboratory tests, and, thus, represents a potential alternative to currently employed biomarkers for the risk classification of advanced solid cancer patients receiving ICI therapies.

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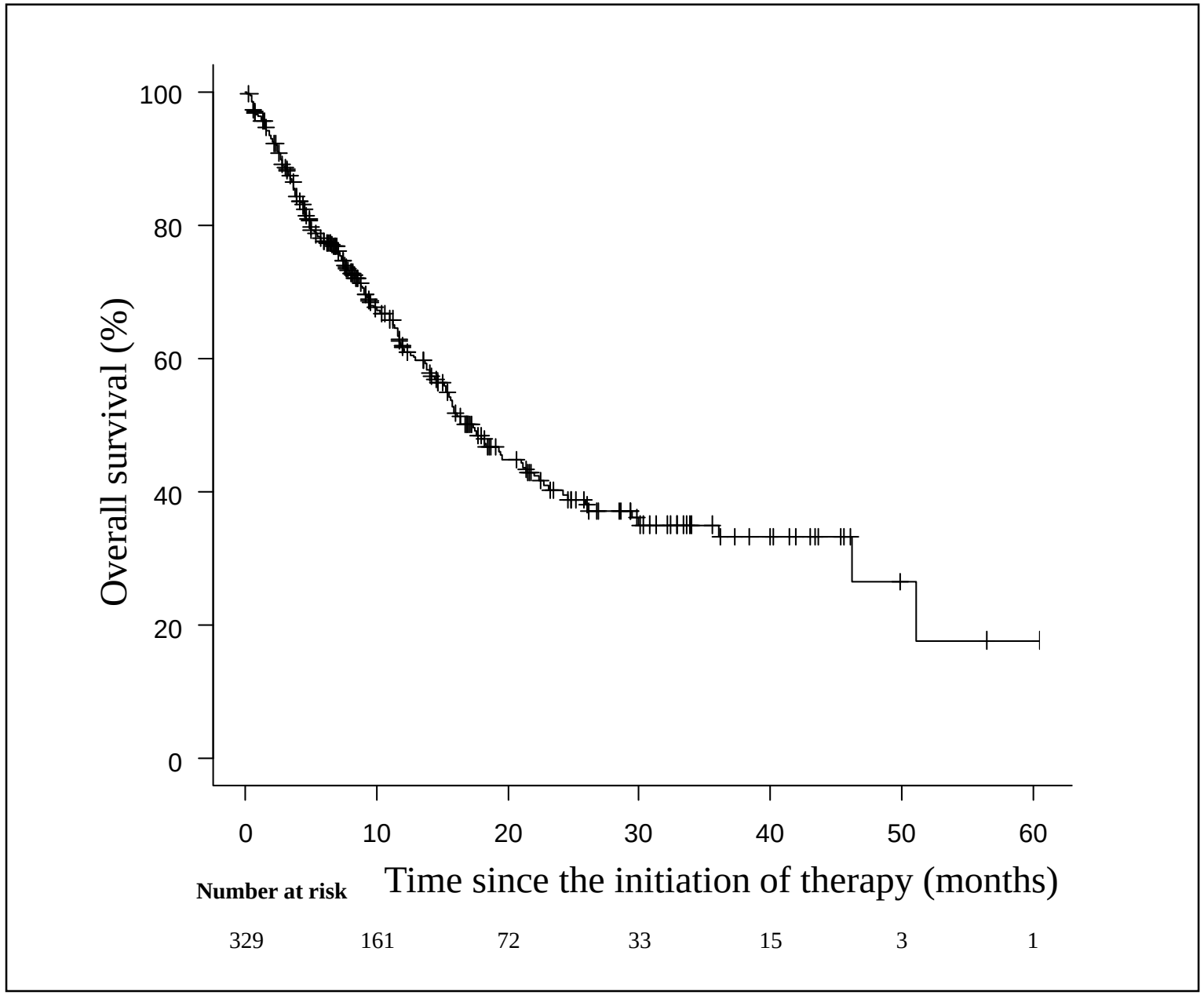
Figure legends

Fig. 1 Overall survival of 329 patients with several advanced solid malignant tumors who received systemic therapy using immune checkpoint inhibitors.

Fig. 2 Overall survival (OS) of 329 patients with several advanced solid malignant tumors who received systemic therapy using immune checkpoint inhibitors according to the number of independent risk factors for OS, including body mass index, C-reactive protein, hemoglobin, neutrophils, and lymphocytes.



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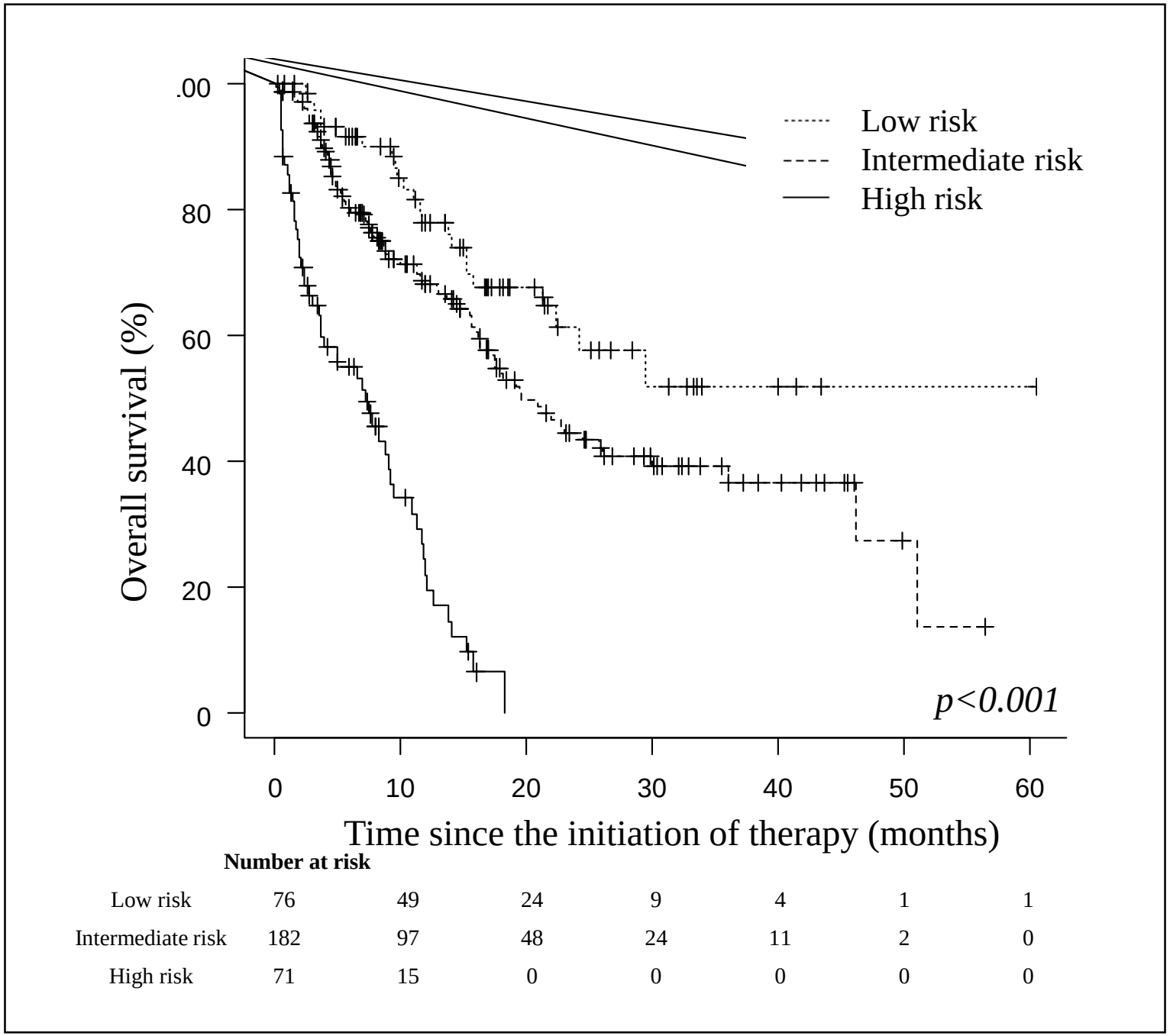

Number at risk

Low risk	76	49	24	9	4	1	1
Intermediate risk	182	97	48	24	11	2	0
High risk	71	15	0	0	0	0	0

Fig. 2 Overall survival (OS) of 329 patients with several advanced solid malignant tumors who received systemic therapy using immune checkpoint inhibitors according to the number of independent risk factors for OS, including body mass index, C-reactive protein, hemoglobin, neutrophils, and lymphocytes.

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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)

Abbreviations: BMI, body mass index

Table 2. Overall survival according to several parameters

Parameter		No. of patients	Median overall survival (months)	*p* value
Age (years)	≤70	151	15.5	0.48
	>70	178	17.6	
Sex	Female	65	15.7	0.45
	Male	244	18.2	
BMI (kg/m^2)	<20	143	15.2	0.0019
	≥20	186	24.2	
Albumin (g/mL)	<3.7	163	13.8	<0.001
	≥3.7	166	23.1	
LDH (U/mL)	≤167	63	NR	0.036
	>167	266	16.2	
CRP (mg/dL)	≤0.96	203	22.7	<0.001
	>0.96	126	8.9	
Hemoglobin (g/dL)	<11.4	144	12.8	<0.001
	≥11.4	185	24.5	
Neutrophils ($10^2/\mu L$)	≤6156	273	19.5	<0.001
	>6156	56	7.8	
Lymphocytes ($10^2/\mu L$)	<1588	256	15.5	<0.001
	≥1588	73	NR	
Platelets ($10^4/\mu L$)	≤24.9	178	21.9	<0.001
	>24.9	151	11.8	
NLR	≤6.8	264	21.4	<0.001
	>6.8	65	7.5	
PNR	≤259	219	22.4	<0.001
	>259	110	11.3	

Abbreviations: BMI, body mass index; LDH, lactate dehydrogenase; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PNR, platelet-to neutrophil ratio; NR, not reached

Table 3. Univariate and multivariable analyses of several parameters 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)	2.234	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