Geriatric nutritional risk index as a predictor of prognosis in metastatic renal cell carcinoma treated with nivolumab

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Abstract

Background: We evaluate the role of the Geriatric Nutritional Risk Index (GNRI) as a prognostic factor in metastatic renal cell carcinoma patients receiving nivolumab.

Methods: Fifty-six consecutive patients with metastatic renal cell carcinoma receiving nivolumab after tyrosine kinase inhibitor between September 2013 and August 2020 at our institution were retrospectively analyzed. The survival outcomes and prognostic factors associated with overall survival (OS) were statistically analyzed.

Results: Median follow-up period was 28.6 months. Median progression-free survival (PFS) and 1- and 3-year PFS rates were 26.4 months, 59.7%, and 19.5%, respectively. Median OS and 1- and 3-year OS rates were 48.1 months, 88.9%, and 74.5%, respectively. Thirteen and forty-three patients were classified with low (GNRI <92) and high (GNRI ≥92) GNRI. Patients with low GNRI demonstrated significantly shorter OS (p = 0.0002) and PFS (p = 0.045) than those with high GNRI. In multivariate analysis, GNRI at the time of nivolumab (hazard ratio: 4.38, p = 0.013) was extracted as the predictor for OS in addition to duration from diagnosis to treatment (p = 0.0005) and lymphocyte count (p = 0.026). Integration of the GNRI into the International Metastatic Renal Cell Cancer Database Consortium (IMDC) risk classification improved the c-index from 0.761 to 0.833 (combination of GNRI with IMDC risk classification) and to 0.778 (substitution of GNRI with Karnofsky performance status in IMDC risk classification).

Conclusions: GNRI was a significant prognostic biomarker in metastatic renal cell carcinoma patients receiving nivolumab. This simple screening tool could be very useful in clinical practice.

Introduction

Nivolumab, which is a fully human IgG4 programmed death 1 (PD-1) antibody, is a novel targeted agent that has been available in clinical practice for the treatment of metastatic renal cell carcinoma (mRCC) since 2016 [1]. Its promising anti-tumor efficacy and manageable safety profile were demonstrated in the phase III Checkmate 025 trial [1], and nivolumab therapy is being rapidly introduced in mRCC clinical practice in Japan. We have previously reported the efficacy and safety profile of nivolumab therapy for Japanese mRCC patients [2]. In real-world clinical practice, it is important to identify the biomarkers that predict the response to nivolumab to achieve a better stratification of patients with mRCC. Some recent reports have suggested that nutritional status is associated with disease development and progression. Nutritional screening tools, such as the prognostic nutritional index [3] and the controlling nutritional index [4], could predict the prognosis of mRCC patients receiving targeted therapy or nivolumab therapy. The Geriatric Nutritional Risk Index (GNRI), which is derived from serum albumin and current/ideal body weight, has been reported as a simplified screening tool to assess the nutrition-related risk associated with mortality in older adult patients as well as those with the various diseases [5]. However, the prognostic value of GNRI in mRCC patients receiving nivolumab therapy remains unclear. In this study, we therefore evaluated the prognostic role of GNRI in mRCC patients treated with nivolumab.

Patients And Methods

Study population

The clinical and labolatory data from 56 consecutive patients with mRCC who were previouly treated with tyrosine kinase inhibitor (TKI) and who started treatment with nivolumab between September 2013 and August 2020 at our institution were retrospectively investigated. Two patients from this cohort had been enrolled in clinical trials. Fifty-two patients had target lesions at the initiation of nivolumab. This study was approved by the Institutional Review Board of the Cancer Institute Hospital, Japanese Foundation for Cancer Research. Before the initial treatment, all patients provided written informed consent for nivolumab treatment. Patients who exhibited disease progression continued nivolumab therapy when a potential clinical benefit with tolerable toxicity was expected.

Treatment And Follow-up Examination

Nivolumab was administrated every 2 weeks as previously described [6]. In Japan, the nivolumab dose was 3 mg/kg until September 2018, when it was changed to 240 mg/body beginning in October 2018. We collected clinical information from medical records, including physical examination, Karnofsky Performance Status (KPS), laboratory findings, and chest radiography before starting treatment and during nivolumab therapy, based on the attending physician's decision. We evaluated the objective response by computed tomography (CT) every 2 or 3 months using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 [7].

Statistical analysis

Descriptive statistics for continuous variables were presented as the median and interquartile range (IQR), and categorical variables were reported as frequencies and percentages. Best overall response was defined as the best response based on the target lesions with CT during nivolumab therapy. Progression-free survival (PFS) and overall survival (OS) periods were defined as the time from initiation of nivolumab to the date of progression and death from any cause, respectively, and these survival curves were estimated using the Kaplan–Meier method. Surviving patients without disease progression and patients lost to follow-up were censored at the time of the last follow-up and last contact. In addition, we investigated the following variables as candidate predictors of prognosis: age, KPS, sex, duration from diagnosis to treatment, blood hemoglobin concentration, corrected serum calcium, platelet count, serum lactate dehydrogenase, neutrophil count, lymphocyte count, line of treatment (third or later line vs. second line), histology (non-clear cell vs. clear cell cancer), International Metastatic Renal Cell Cancer Database Consortium (IMDC) risk classification, GNRI at the time of nivolumab, and number of metastatic lesions. GNRI was calculated as follows: GNRI= [1.489 × albumin (g / L)] + [41.7 × (weight / ideal body weight)] [8]. The ideal body weight was defined as the value calculated from the height and body mass index (BMI) of 22 [9], and the body weight/ideal body weight was set to 1, when the patient's body weight

exceeded the ideal body weight. According to the previously proposed criterion [10], GNRI ≥ 92 was defined as high GNRI, meaning no or low nutritional risk, whereas GNRI < 92 was defined as low GNRI, meaning moderate or severe nutritional risk. A chi-squared test was used to compare between the objective response rate (ORR) and the categorical covariates as the univariate analysis, and to assess the relationship between GNRI and IMDC risk classification. The log-rank test and generalized Wilcoxon test were performed to compare the difference in PFS and OS between each group. Using a univariate and multivariate Cox proportional hazards model, the significant association between OS and clinical factors was investigated. The predictive accuracy of GNRI and IMDC risk classification was calculated according to Harrell's concordance index (C-index). The hazard ratio (HR) and 95% confidence interval were calculated as the predictor for OS. All of the statistical analyses were performed using JMP software version 14.0 (SAS Institute Inc., Cary, NC, USA), and p values < 0.05 were considered statistically significant.

Results

Patient characteristics

The median follow-up period was 28.6 (IQR, 13.9–39.7) months after initiation of nivolumab. Patient characteristics are described in Table 1. Thirteen (23%) and one (2%) patients died as a result of disease progression and other causes, respectively. The remaining 42 patients (75%) survived and, among these patients, 36 (86%) were alive at least 1 year after the initiation of nivolumab. Forty-one, twelve, and three patients were administered nivolumab as second-, third-, and fourth-line therapies, respectively. In terms of GNRI [2], the number of high and low GNRI patients was 43 (77%) and 13 (23%), respectively. The number of patients with favorable, intermediate, and poor risk as determined by the IMDC risk classification [1] was 21 (38%), 27 (48%), and 8 (14%), respectively. Although the GNRI tended to be lower as the IMDC risk classification grew higher, there was no significant difference (p = 0.124) (Table 2).

Table 1
Patient characteristics (n = 56)

Clinical factors			Number
Median age, years (inter-quartile range)			62 (56–69)
Sex	Male		42 (75)
	Female		14 (25)
Karnofsky Performance Status (%)	< 80		3 (5)
	≥ 80		53 (95)
Histology (%)	Clear cell		49 (87)
	Papillary	Type 1	1 (2)
		Type 2	2 (4)
		Unknown	1 (2)
	Unclassified		3 (5)
Duration of 1st -line therapy, months (%)	< 12		28 (50)
	≥ 12		28 (50)
Number of metastatic lesions (%)	< 2		25 (44)
	≥ 2		29 (52)
Number of treatment lines (%)	< 2		41 (73)
	≥ 2		15 (27)
IMDC risk classification (%)	Favorable		21 (38)
	Intermediate		27 (48)
	Poor		8 (14)
GNRI (%)	< 92		13 (23)
	≧ 92		43 (77)

IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; GNRI: Geriatric Nutritional Risk Index

Table 2
Association between GNRI and IMDC risk classification (n = 56)

		IMDC risk classification, n (%)			
		Favorable	Intermediate	Poor	Total
GNRI	High	18 (86)	21 (78)	4 (50)	43
	Low	3 (14)	6 (22)	4 (50)	13
	Total	21 (100)	27 (100)	8 (100)	56
$p = 0.124$					

IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; GNRI: Geriatric Nutritional Risk Index

Efficacy Of Nivolumab Therapy

Overall, 52 patients were evaluable for response, excluding 4 patients who had non-target lesions based on the RECIST guidelines. The ORR was 35% (complete response [CR], 3 patients [5%] and partial response [PR], 17 patients [30%]). Stable disease (SD) was present in 25 patients (45%) and progressive disease (PD) was present in 10 patients (18%) as the best response to nivolumab. The ORR was 34% (14/41) and 40% (6/15) in patients with nivolumab as a second- and third- or later line therapy; 31% (15/49) and 71% (5/7) in those with clear cell and non-clear cell cancer; 24% (5/21), 44% (12/27) and 38% (3/8) in those with favorable, intermediate, and poor risk in IMDC risk classification; and 31% (4/13) and 37% (16/43) in those with low and high GNRI ($p = 0.56$), respectively (Fig. 1a). From the initiation of nivolumab, median PFS and 1- and 3-year PFS rates were 26.4 months, 59.7%, and 19.5%, respectively (Fig. 1b). Median OS and 1- and 3-year OS rates were 48.1 months, 88.9%, and 74.5%, respectively (Fig. 1c). Application of the prognostic model using GNRI revealed the significant difference in PFS ($p = 0.045$) and OS ($p = 0.0002$) between low and high GNRI. Median PFS, 1- and 3-year PFS rates and median OS, 1- and 3-year OS rates in low vs. high GNRI were 7.5 vs. 31.8 months, 39.5 vs. 66.0% and 0 vs. 25.7%, and 32.8 vs. 48.1 months, 55.9 vs. 97.7% and 42.0 vs. 83.6%, respectively (Fig. 2a, b).

Predictors Of Prognosis In Nivolumab Therapy

We investigated the predictors of prognosis in nivolumab therapy among the pre-treatment variables. In multivariate analysis, GNRI at the time of nivolumab (HR: 4.38, $p = 0.013$), duration from diagnosis to treatment (HR: 9.33, $p = 0.0005$), and lymphocyte count (HR: 4.46, $p = 0.026$) were extracted as the predictors for overall survival (Table 3). The c-index of GNRI for predicting OS was 0.693 (95% CI: 0.626, 0.760). The c-index of GNRI combined with IMDC risk classification was improved compared with IMDC risk classification alone (0.833 [95% CI: 0.786, 0.880] vs. 0.761 [95% CI: 0.714, 0.808]). When GNRI was substituted for KPS in IMDC risk classification, the c-index was improved from 0.761 to 0.778 (95% CI:

0.726, 0.830). Application of the prognostic model using three factors, including GNRI, duration from diagnosis to treatment, and lymphocyte count, revealed distinctly separate OS curves for groups between Score 0 and 1–2 ($p = 0.0065$), and Score 1–2 and 3 ($p < 0.0001$) (Fig. 3, $p < 0.0001$). The median OS, 6-month, 1-, and 3-year OS rates for Score 0 were not reached, 100%, 100%, and 94.4%; those for Score 1–2 were 48.1 months, 93.0%, 89.3%, and 66.3%; and those for Score 3 were 5.4 months, 33.3%, 0%, and 0%, respectively.

Table 3
Comparison of overall survival in the risk factors for nivolumab

Variables		Univariate		Multivariate	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)	< 65 vs. ≥65	1.11 (0.38, 3.64)	0.846		
Karnofsky Performance Status	< 80 vs. ≥80	12.4 (2.58, 47.99)	0.0037		
Sex	female vs. male	1.14 (0.27, 3.92)	0.842		
Duration from diagnosis to treatment (years)	< 1 vs. ≥1	10.5 (2.85, 67.50)	0.0001	9.33 (2.47, 60.90)	0.0005
Hemoglobin	<LLN vs. ≥LLN	3.11 (1.07, 10.16)	0.037		
Corrected serum calcium (mg/dl)	≥ 10 vs. <10	1.87 (0.10, 9.50)	0.583		
Platelet (cell count/μl)	≥ 400×10^3 vs. <400×10^3	2.30 (0.13, 11.74)	0.476		
LDH (U/l)	≥ULN vs. <ULN	4.55 (1.46, 13.77)	0.011		
Neutrophil (cell count/μl)	≥ 4000 vs. <4000	2.68 (0.89, 8.33)	0.077		
Lymphocyte (cell count/μl)	< 1000 vs. ≥1000	4.04 (1.20,12.34)	0.026	4.46 (1.21, 15.98)	0.026
Line of treatment	third- or later line vs. second-line	1.65 (0.54, 4.78)	0.366		
Histology	Non-clear vs. clear	1.08 (0.17, 4.06)	0.919		
IMDC risk classification	Poor vs. favorable/intermediate	5.41 (1.71, 16.05)	0.006		
GNRI at the time of nivolumab	< 92 vs. ≥92	6.17 (2.03, 19.35)	0.0018	4.38 (1.38, 14.27)	0.013

CI: confidence interval; HR: hazard ratio; LDH: lactate dehydrogenase; LLN: lower limit of normal range; ULN: upper limit of normal range;

IMDC: International Metastatic renal cell cancer Database Consortium classification; GNRI: Geriatric Nutritional Risk Index

Variables		Univariate		Multivariate	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Number of metastatic lesions	< 2 vs. ≥2	1.07 (0.37, 3.25)	0.902		
CI: confidence interval; HR: hazard ratio; LDH: lactate dehydrogenase; LLN: lower limit of normal range; ULN: upper limit of normal range;					
IMDC: International Metastatic renal cell cancer Database Consortium classification; GNRI: Geriatric Nutritional Risk Index					

Discussion

We previously demonstrated the therapeutic outcomes and safety profiles in Japanese patients with mRCC after TKI in real-world clinical practice [2]. Although the efficacy of nivolumab therapy for mRCC is not in doubt, as shown in Fig. 1A-C, it is not effective in all patients. Therefore, it is important to identify the prognostic factors that predict the response of nivolumab to achieve a better stratification of patients with mRCC. In this study, we reported that PFS and OS in mRCC patients with high GNRI treated with nivolumab were significantly better than those with low GNRI. To the best of our knowledge, this is the first report to show the effectiveness of GNRI as a prognostic biomarker in nivolumab therapy for mRCC.

The association of the prognosis of patients with RCC with systemic inflammation was previously reported. When they investigated the impact of the risk group disagreement between the Memorial Sloan Kettering Cancer Center (MSKCC) and IMDC classifications on prognosis, it was determined that disagreement between both classifications may have a negative impact on prognosis in mRCC patients because of the inclusion of systematic inflammation markers [5]. Another report also suggested that the combination of C-reative protein (CRP) value with the number of risk factors in the IMDC classification might achieve better stratification of prognosis in patients with IMDC intermediate risk treated with TKI [11]. We previously reported that modified Glasgow Prognostic Score based on serum albumin as a nutritional status indicator and CRP was a significant prognostic biomarker in mRCC treated with nivolumab [12]. Thus, nutritional status also plays a key role in predicting the prognosis of mRCC patients. Sarcopenia was also suggested to be a prognostic factor for patients with mRCC [13] and those receiving treatment by surgery [14] and TKI [15]. The effective prevention and treatment of sarcopenia was reported to be achieved by improving diet and nutrition [16]. Cancer-associated cachexia is characterized by severe loss of muscle mass with or without loss of fat [17] and is associated with increased morbidity and mortality, especially interleukin-6 levels correlating with weight loss in certain human cancers [18]. Therefore, a simple nutritional screening tool that can act as a prognostic marker for mRCC patients treated with nivolumab is needed, because the association of the nutritional index with the prognosis of mRCC patients was suggested.

GNRI was reported to be a new simplified screening tool to assess the nutrition-related risk that has been shown to be associated with mortality in older adult patients as well as those with various diseases [8, 19, 20]. Recently, GNRI has been reported to be associated with the prognostic factor of undergoing nephrectomy [21] and being treated with targeted therapy [22]. However, there have been no reports suggesting the association of GNRI with the prognosis of mRCC patients treated with nivolumab therapy, although the association of GNRI with prognosis in patients with non-small cell lung cancer treated with nivolumab therapy has been reported [23].

Some reports have suggested that patients with weight gain achieved better survival outcomes. PFS and OS as well as ORR were significantly better in overweight patients that had a BMI $\geq$ 25 with various cancers treated with anti-PD-1/programmed death-ligand 1 inhibitors [24]. A higher BMI and weight gain during nivolumab therapy were good predictive markers of OS in mRCC patients receiving nivolumab therapy [25]. The better survival outcomes in overweight patients are related to the white adipose tissue, which induces and/or coordinates host defenses, being a source of cytokines and chemokines [26]. Adipose tissue modulates the helper T-cell (Th)1/Th2 balance, decreases the activation of regulatory T-cell through adiponectin, increases pro-inflammatory macrophages, activates T-cells with the binding between LIGHT-HVEM (herpesvirus entry mediator), and increases the inflammatory status through the CD40 pathway [27–29].

Some reports suggested that pre-treatment albumin level was also associated with prognosis in mRCC patients. Lower serum albumin has been reported to be related with poorer OS and PFS in mRCC patients treated with targeted therapy [30]. Another report suggested that a lower albumin to alkaline phosphatase ratio was associated with worse OS and PFS in mRCC patients receiving nivolumab monotherapy [31]. As one of the reasons for the association between albumin and prognosis in mRCC patients, the formation of neutrophil extracellular traps, which are released to the tumor microenvironment by cancer cells to recruit neutrophils and which play a key regulatory role in cancer aggressiveness, such as cancer invasion and distant metastases [32], was inhibited by serum albumin [33].

Therefore, GNRI was suggested to be the prognostic factor for mRCC patients treated with nivolumab therapy in our study. GNRI, which is a simple nutritional screening tool, combined with IMDC risk classification or substituted for KPS in IMDC risk classification, could provide improved stratification for the prognosis of mRCC patients receiving nivolumab therapy in real-world clinical practice.

We conducted this retrospective study to clarify the effectiveness of GNRI in nivolumab therapy. There are several limitations to our study. First, this was a small, retrospective study at a single institution. Additional large-scale and/or prospective studies are needed to clarify the effectiveness of GNRI in nivolumab therapy. Second, all cases were treated with nivolumab therapy as a second-line or later therapy, rather than as a first-line therapy. GNRI as a first-line targeted therapy was also shown to have a significant difference in OS for mRCC patients compared to the previous study [22]. Therefore, these pre-treatment variables, which include body weight and albumin at baseline, may be influenced by the previous first-line therapy.

In conclusion, the present study demonstrated that GNRI was a significant prognostic biomarker in mRCC patients treated with nivolumab. This simple classification might be useful in clinical practice. Our preliminary findings from a retrospective, single-institutional cohort require future external validation.

Abbreviations

PD-1
programmed death 1
mRCC
metastatic renal cell carcinoma
GNRI
Geriatric Nutritional Risk Index
TKI
tyrosine kinase inhibitor
KPS
Karnofsky Performance Status
CT
computed tomography
RECIST
Response Evaluation Criteria in Solid Tumors
IQR
interquartile range
PFS
progression-free survival
OS
overall survival
IMDC
International Metastatic Renal Cell Cancer Database Consortium
BMI
body mass index
ORR
objective response rate
C-index
Harrell’s concordance inde
HR
hazard ratio
CR
complete response
PR
partial response

SD
Stable disease
PD
progressive disease
MSKCC
Memorial Sloan Kettering Cancer Center
CRP
C-reative protein
Th
helper T-cell

Declarations

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Authors' contributions

Conception and design: RF, TY, SY, administrative support: TY, JY, collection and assembly of data:RF, TY, data analysis and interpretation:RF, MF manuscript writing: RF. All authors fnal approval of manuscript.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Cancer Institute Hospital, Japanese Foundation for Cancer Research. (C-T2020-0381) and all patients signed the preoperative informed consent.

Competing interests

T. Yuasa received remuneration for a lecture from Astellas (Tokyo, Japan), Sanofi Japan (Tokyo, Japan), Pfizer Japan (Tokyo, Japan), Novartis Pharma Japan (Tokyo, Japan), Ono Pharma (Osaka, Japan), Bristol-Myers Squibb Japan (Tokyo, Japan), Janssen Pharmaceutical K.K Japan (Tokyo, Japan), MSD Japan (Tokyo, Japan), and Daiichi-Sankyo (Tokyo, Japan). The other authors have declared no conflicts of interest.

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Figures

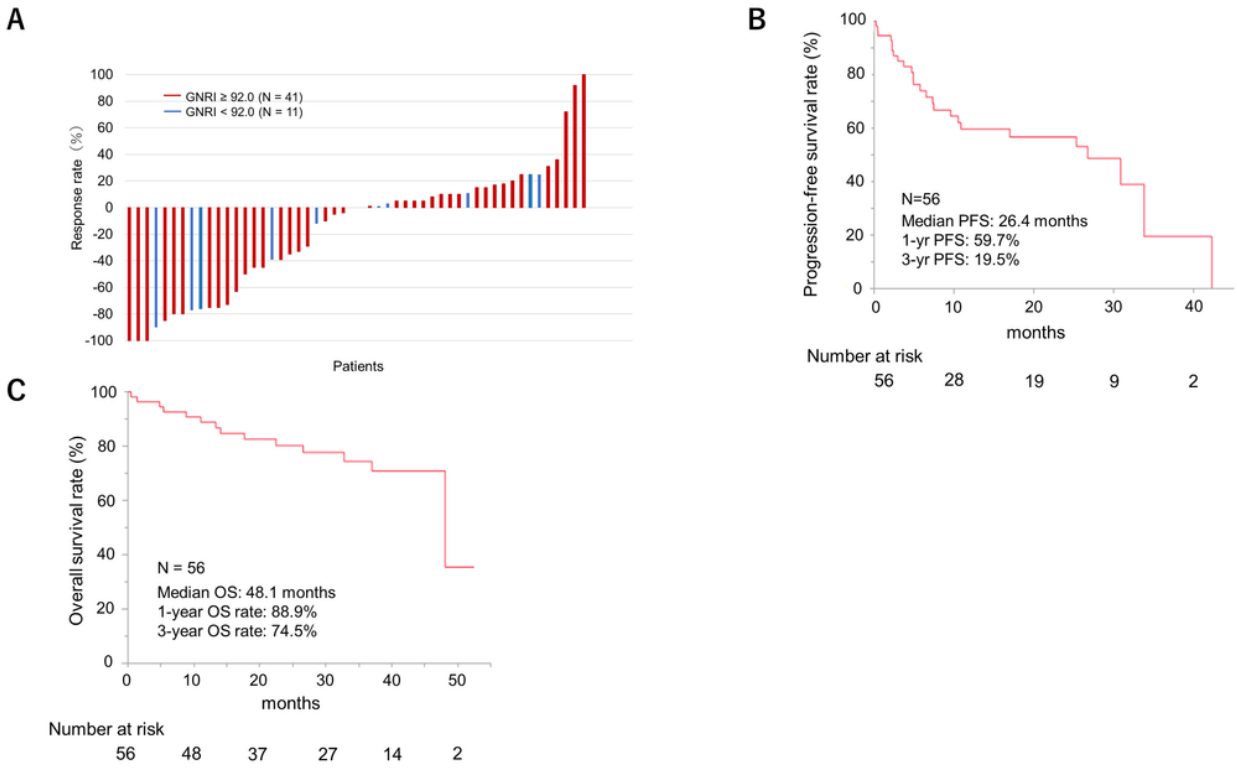

Figure 1

Efficacy of nivolumab for patients with metastatic renal cell cancer. Waterfall plots of the response to nivolumab (a, n = 52). Progression-free survival and overall survival curves (b, c, n = 56).

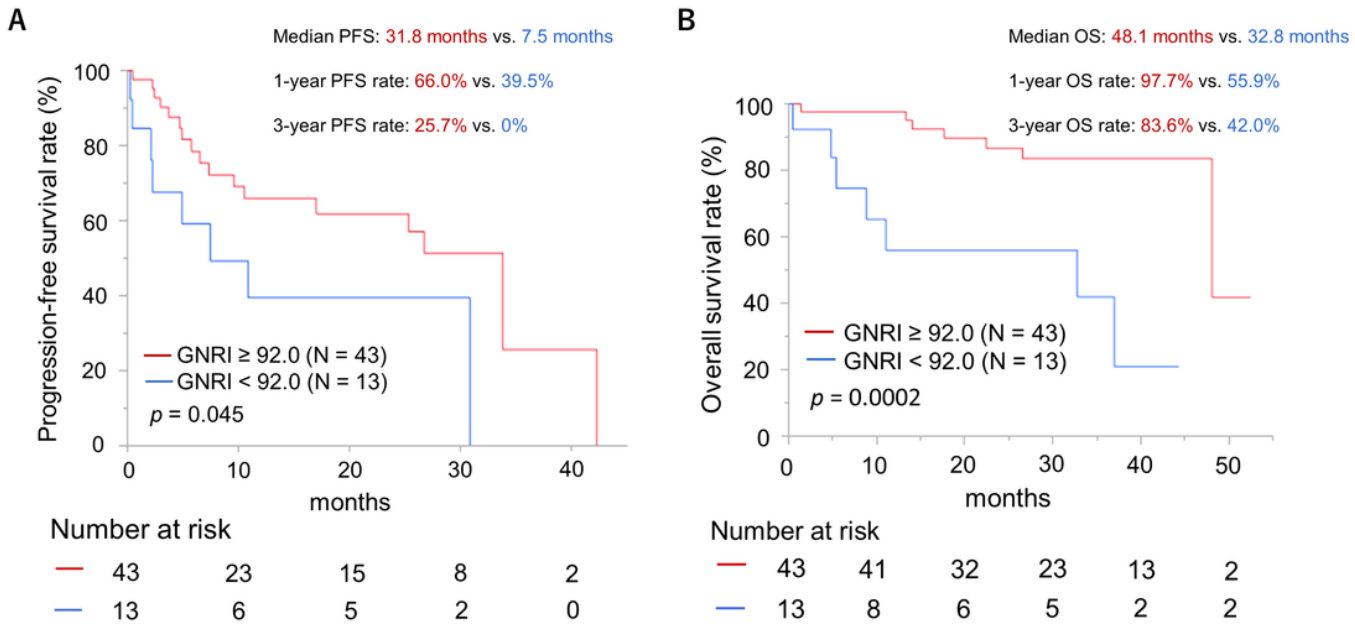

Figure 2

Progression-free survival and overall survival curves divided by the prognostic model using GNRI (a, b, GNRI ≥ 92 [n = 43], GNRI < 92 [n = 13]).

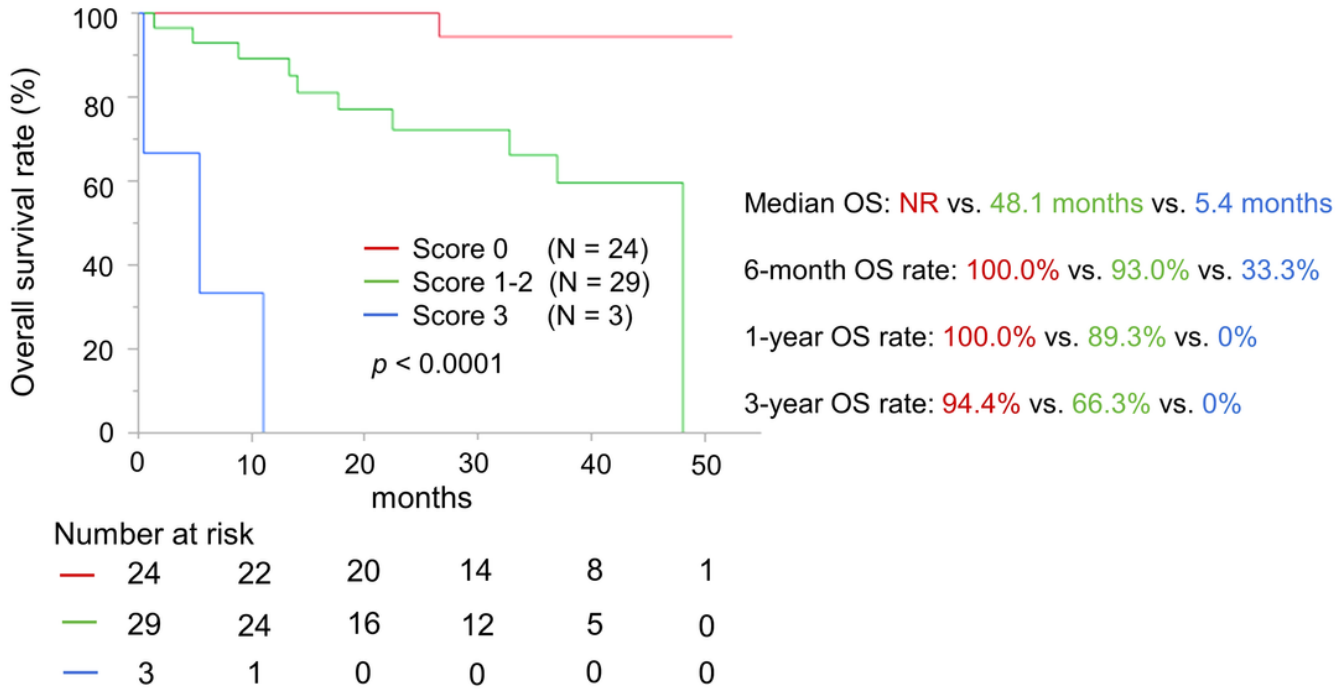

Figure 3

Overall survival curves divided by the prognostic model using three factors, including GNRI, duration from diagnosis to treatment, and lymphocyte count (Score 0 [n = 24], Score 1-2 [n = 29], Score 3 [n = 3]).