Prognostic model including the combination of platelet count and neutrophil–lymphocyte ratio for metastatic renal cell carcinoma treated with sunitinib

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Abstract

Background

The association between the combination of platelet count and neutrophil–lymphocyte ratio (COP-NLR) at the time of adverse events during sunitinib treatment and prognosis is unclear, and prognostic models combining the prognostic factors of sunitinib have not been well studied. To develop a prognostic model that includes the COP-NLR to predict the prognosis of patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib.

Methods

We performed a retrospective cohort study of 102 patients treated with sunitinib for mRCC between 2008 and 2020 in three hospitals associated with Showa University, Japan. The primary outcome was overall survival (OS). The collected data included baseline patient characteristics, adverse events, laboratory values, and COP-NLR scores within the first 6 weeks of sunitinib treatment. Prognostic factors of OS were analyzed using the Cox proportional hazards model. The integer score was derived from the hazard ratio (HR) of these factors and was divided into three groups. The survival curves were visualized using the Kaplan–Meier method and estimated using a log-rank test.

Results

The median OS was 32.3 months. Multivariate analysis showed that the number of metastatic sites, Memorial Sloan Kettering Cancer Center risk group, number of metastases, hypertension, modified Glasgow Prognostic Score, and 6-week COP-NLR were significantly associated with OS. A higher 6-week COP-NLR was significantly associated with a shorter OS ($p < 0.001$). The HRs of the five factors for OS were scored (hypertension, mGPS, and 6-week COP-NLR=1 point; number of metastatic sites=2 points; MSKCC risk group=3 points) and patients divided into three groups (≤1, 2–3, and ≥4). The low-risk (≤1) group had significantly longer OS than the high-risk (≥4) group (median OS: 99.0 vs 6.2 months, $p < 0.001$).

Conclusions

The 6-week COP-NLR, which was associated with OS, was an important prognostic factor in patients with mRCC treated with sunitinib. The developed prognostic model for OS, including the 6-week COP-NLR, will be useful in decision-making to continue sunitinib in the early treatment stage of patients with mRCC.

Background

Renal cell carcinoma (RCC) accounts for 5% of all cancers in men and 3% of cancers in women worldwide, representing the 6th and 10th most frequently diagnosed cancers, respectively [1, 2]. The 5-year survival rate is 74% overall, decreasing to 8% among patients with metastatic disease (stage IV) [3, 4]. Early-stage RCC is often asymptomatic, although the presence of systemic symptoms is frequently associated with advanced or metastatic RCC (mRCC).

The treatment selection for patients with mRCC widely uses the Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium model. The advent of immune checkpoint inhibitors has broadened the treatment options for mRCC. Although sunitinib is the first-line therapy for patients with favorable or intermediate-risk mRCC, it must be discontinued if it causes severe myelosuppression. However, it has been reported that long-term treatment with sunitinib at a dose that reduces tumor size in the early stage is critical to maximize the potential efficacy of sunitinib treatment [5]. Therefore, determining the clinical benefit of continuing sunitinib prior to the occurrence of serious adverse events (AEs) leads to an appropriate treatment option for mRCC.

Previous studies have reported that C-reactive protein (CRP), MSKCC model, modified Glasgow Prognostic Score (mGPS), and malnutrition are significantly associated with prognostic factors for progression-free survival (PFS) and overall survival (OS) of mRCC treated with sunitinib [6–11]. Additionally, sunitinib-induced hypertension, neutropenia, and thrombocytopenia have been reported as predictors of sunitinib efficacy [12–15]. Moreover, one study has developed prognostic models by combining the prognostic factors of sunitinib [7].

On the other hand, the combination of platelet count and neutrophil–lymphocyte ratio (COP-NLR), which is calculated using inflammatory markers such as the NLR and platelet count, has been shown to be useful as a prognostic factor in gastrointestinal cancer and non-small cell lung cancer [16–21]. The COP-NLR before surgery or targeted therapy has also been associated with prognosis in patients with RCC [22, 23]. Additionally, the COP-NLR values are affected by neutropenia and thrombocytopenia as AEs related to sunitinib treatment. In particular, these AEs are more likely to occur within the first 6 weeks of sunitinib treatment.

However, the association between the COP-NLR at the time of AEs during sunitinib treatment and prognosis is unclear, and models combining the prognostic factors of sunitinib have not been well studied. If a prognostic model could be developed, the clinical benefit of continuing sunitinib in the early stage could be determined, leading to the avoidance of serious AEs and longer survival based on long-term treatment with sunitinib. Therefore, we investigated the prognostic factors, including the COP-NLR at the time of AEs within the first 6 weeks of sunitinib treatment, and developed a prognostic model to predict the prognosis of patients with mRCC treated with sunitinib.

Methods

1 Study patients

We performed a retrospective cohort study of 102 patients treated with sunitinib for mRCC at Showa University Hospital, Showa University Northern Yokohama Hospital, and Showa University Fujigaoka Hospital, between 1 June 2008 and 31 December 2019. The data collection limit date was 30 September 2020. All patients were diagnosed with mRCC based on computed tomography (CT)/magnetic resonance imaging (MRI), and, when appropriate, brain imaging, and bone scintigraphy. This study was approved by the Ethics Committee of the Showa University School of Pharmacy.

2 Collection of patient data

Data were collected from medical records at the baseline. AEs within the first 6 weeks of sunitinib treatment were collected. Laboratory values within the first 6 weeks of sunitinib treatment were collected at the lowest platelet count based on the occurrence of thrombocytopenia, which has been reported to be a predictor of sunitinib efficacy [13].

2.1 Patient characteristics

The patient background data included sex, age, Eastern Cooperative Oncology Group performance status (PS), histology type, prior nephrectomy, metastatic sites, number of metastatic sites, MSKCC risk groups (favorable-, intermediate-, and poor-risk groups), prior treatment (immunotherapy, targeted therapy), and treatment (first-, second-, and third-line). The drug-related data included the initial dose of sunitinib, treatment schedule, relative dose intensity (RDI) during the first 6 weeks of sunitinib treatment (6-week RDI), and duration of therapy. Blood test data included aspartate aminotransferase (AST), albumin (Alb), CRP, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), mGPS, and COP-NLR.

2.2 Definitions

The MSKCC model was based on five pretreatment variables (Karnofsky PS, LDH concentration, hemoglobin concentration, serum calcium concentration, and time from initial diagnosis to start of systemic treatment) and divided into three risk groups: favorable-risk (0 risk factor), intermediate-risk (1,2 risk factors), and poor-risk (≥3 risk factors) groups. Hypertension was defined as ≥140/90 mm Hg. Hypothyroidism was defined as elevated thyroid-stimulating hormone levels with normal triiodothyronine and thyroxine levels. mGPS was defined as follows: patients with elevated CRP levels (>0.5 mg/dL) and hypoalbuminemia (<3.5 g/dL) were allocated mGPS 2, patients with only one factor were allocated mGPS 1, and patients with neither factor were allocated mGPS 0. The COP-NLR was defined as follows: patients with elevated platelet levels (>310 × 10^9/L) and NLR >3.5 were allocated COP-NLR 2, patients with only one factor were allocated COP-NLR 1, and patients with neither factor were allocated COP-NLR 0.

2.3 Division

CRP and Alb levels were divided into two groups according to the lower limit of normal values. AST and ALP levels were divided into two groups according to the upper limit of the normal values. LDH was divided into two groups based on the LDH levels (333 U/L) of the MSKCC model. mGPS and COP-NLR were divided into two groups: moderate (score, 1) or higher.

2.4 Assessment of response

The response was assessed by CT/MRI performed at 2- to 3- month intervals. Treatment efficacy was reported according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1.

2.5 Adverse events

The following AEs related to sunitinib treatment were collected: hypertension, hand-foot syndrome, stomatitis, dysgeusia, oedema, nausea/vomiting, hemorrhage, constipation, diarrhea, fatigue, hypothyroidism, leukopenia, thrombocytopenia, anemia, elevation of AST, elevation of serum creatinine, and elevation of ALP. AEs related to sunitinib treatment were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

3 Outcome

The primary outcomes were time to treatment failure (TTF), PFS, and OS. Tumor progression was evaluated based on progressive disease using RECIST.

Time-to-event variables were estimated using the Kaplan–Meier method. TTF was defined as the duration from the first day of sunitinib treatment until the date of discontinuation of sunitinib treatment or death from any cause, whichever came first. PFS was defined as the duration from the first day of sunitinib treatment to the date of tumor progression or death from any cause or the last follow-up visit, whichever came first. OS was defined as the duration from the first day of sunitinib treatment to the date of death from any cause or the last follow-up visit.

4 Statistical analysis

4.1 The Kaplan–Meier method

Survival curves were estimated using the Kaplan–Meier method. The log-rank test was used to compare survival times between the two groups.

4.2 Univariate and multivariate analyses

Univariate and multivariate analyses were performed using the Cox proportional hazards model. Significant variables ($p < 0.05$) extracted by a univariate analysis were entered into the multivariate analysis. Significant independent variables contributing to the prognosis of patients with mRCC treated with sunitinib were extracted using a stepwise selection method.

4.3 Prognostic model and assessment

Each prognostic model was developed using prognostic factors extracted by multivariate analysis. The hazard ratios (HRs) for these factors were derived from the smallest HR among the prognostic factors, approximated to the nearest integer. For each factor, the approximate HRs were scored as integers. For each patient, the scores were calculated as the sum of the scores for each factor. Patients were divided into three groups (low-, intermediate-, and high-risk) based on the distribution of their scores. Survival curves of the three groups were estimated using the Kaplan–Meier method. The log-rank test was used to compare survival times among the three groups in prognostic models for TTF, PFS, and OS. All statistical analyses were performed using the SPSS software, version 27 (IBM, Tokyo, Japan). Statistical significance was set at $P < 0.05$.

Results

1 Patient characteristics

The characteristics of the 102 patients are shown in Table 1. The median age was 67.5 (range, 28–83) years, and 83 (81.4%) were males. The MSKCC risk groups were favorable in 13 patients (12.8%), intermediate in 70 (68.6%), and poor in 19 (18.6%). The median follow-up period was 23.6 (range, 0.2–135.3) months. The median duration of sunitinib treatment was 4.7 (range, 0.2–67.1) months. Seventy-five patients (73.5%) received sunitinib for at least 6 weeks.

2 Outcome

The cumulative survival curve for all patients is shown in Fig. 1. The median TTF, PFS, and OS were 4.9, 5.8, and 32.3 months, respectively. During the follow-up period, 17 patients (16.7%) discontinued sunitinib due to AEs, 87 patients (85.3%) experienced disease progression, and 55 patients (53.9%) died of any cause.

3 Univariate and multivariate analyses

The results of univariate and multivariate analyses are summarized in Table 2. Among the factors that were significant in the univariate analysis, multivariate analysis was performed, except for those that were correlated. In the multivariate analysis, the number of metastatic sites, AST, ALP, 6-week RDI, and 6-week COP-NLR were significantly associated with TTF. Additionally, the number of metastatic sites, MSKCC risk group, hand-foot syndrome, and 6-week COP-NLR were significantly associated with PFS. Moreover, the number of metastatic sites, MSKCC risk group, hypertension, mGPS, and 6-week COP-NLR were significantly associated with OS.

4 Survival curves according to the 6-week COP-NLR

The Kaplan–Meier curves of TTF, PFS, and OS according to the 6-week COP-NLR are shown in Fig. 2. A higher 6-week COP-NLR was significantly associated with shorter TTF, PFS, and OS ($p < 0.001$).

5 Prognostic model and assessment

The integer scores assigned from the HR of prognostic factors for TTF were as follows: 1 point for the number of metastatic sites, AST, ALP, and 6-week COP-NLR; and 2 points for 6-week RDI. The sum of the scores of the five factors, ranging from 0 to 6, was calculated for all patients. The patients were divided into three groups: low-risk group (≤1 point; n = 37), intermediate-risk group (2-3 points; n = 36), and high-risk group (≥4 points; n = 20). Additionally, the integer scores assigned from the HR of prognostic factors for PFS were as follows: 1 point for the number of metastatic sites, hand-foot syndrome, and 6-week COP-NLR; and 2 points for MSKCC risk group. The sum of the scores of the five factors, ranging from 0 to 5, was calculated for all patients. The patients were divided into three groups: low-risk group (≤1 point; n = 48), intermediate-risk group (2-3 points; n = 26), and high-risk group (≥4 points; n = 22). Moreover, the integer scores assigned from the HR of prognostic factors for OS were as follows: 1 point for hypertension, mGPS, and 6-week COP-NLR; 2 points for the number of metastatic sites; and 3 points for the MSKCC risk group. The sum of the scores of the five factors, ranging from 0 to 8, was calculated for all patients. The patients were divided into three groups: low-risk group (≤1 point; n = 30), intermediate-risk group (2-3 points; n = 32), and high-risk group (≥4 points; n = 34).

The Kaplan–Meier curves of TTF, PFS, and OS according to the prognostic models are shown in Fig. 3. There were significant differences among the three groups in the prognostic models for TTF, PFS, and OS ($p < 0.001$).

6 Adverse events

The most common treatment-related AEs associated with sunitinib are shown in Table 3. The most common AEs of all grades were hypertension in 60 patients (58.8%), hand-foot syndrome in 49 (48.0%), leukopenia in 55 (53.9%), and thrombocytopenia in 79 (77.5%). The most common grade 3/4 AEs were hypertension in 20 patients (19.6%), hand-foot syndrome in 7 (6.9%), leukopenia in 10 (9.8%), and thrombocytopenia in 17 (16.7%).

Discussion

In this study, we first demonstrated that the 6-week COP-NLR, which was associated with TTF, PFS, and OS, was an important prognostic factor in patients with mRCC treated with sunitinib. Neutropenia and thrombocytopenia related to sunitinib treatment are more likely to occur within the first 6 weeks of sunitinib treatment. These AEs are predictors of sunitinib efficacy and are components of the COP-NLR [13].

To the best of our knowledge, this is the first study to reveal the relationship between the 6-week COP-NLR and prognosis, including the effects of neutropenia and thrombocytopenia. Additionally, there have been few reports on clinical criteria for the continuation of sunitinib treatment, including laboratory values that were affected by AEs of sunitinib, such as the 6-week COP-NLR. Therefore, this study had a high clinical application value. Moreover, we showed that the developed prognostic models for TTF, PFS, and OS accurately predicted the prognosis of patients with mRCC treated with sunitinib ($p < 0.001$). Therefore, these models may provide clinical criteria for the continuation of sunitinib treatment in the early stages of mRCC.

This study showed that the COP-NLR within the first 6 weeks of sunitinib treatment had a greater impact on OS than COP-NLR at the start of sunitinib treatment. The higher 6-week COP-NLR indicated that sunitinib did not reduce the number of platelets and neutrophils in the blood. Sunitinib exhibits a dose- and time-dependent antitumor effect [24]. In the absence of the occurrence of thrombocytopenia, the antitumor effect of vascular endothelial growth factor receptor (VEGFR) inhibition is not achieved and may lead to a shorter OS. In tumor progression, neutrophils and lymphocytes, which are components of the COP-NLR, are associated with the tumor microenvironment. Neutrophils are involved in tumor progression, and lymphocytes play a role in antitumor immunity [25]. Platelets induce epithelial-to-mesenchymal transition in cancer and promote metastasis from the primary site [26]. Angiogenic factors and growth factors released from platelets promote tumor angiogenesis, tumor growth, and metastasis [27]. Therefore, in the absence of neutropenia or thrombocytopenia, cytokines released from neutrophils may cause tumor growth and progression. Additionally, angiogenic and growth factors released from platelets promote tumor angiogenesis, and tumor growth may lead to a poor prognosis.

In addition to the 6-week COP-NLR, the MSKCC risk group, number of metastases, hypertension, and mGPS were significantly associated with OS. Poor PS and poor nutritional status have been reported as poor prognostic factors for sunitinib [6, 8]. Therefore, poor PS and poor nutritional status due to the high number of metastases and poor MSKCC risk group may have affected OS. Additionally, sunitinib-induced hypertension is correlated with the effects of VEGFR inhibition [12]. In the absence of the occurrence of hypertension, the effect of VEGFR inhibition is not achieved and may lead to a shorter OS.

In this study, we also investigated the impact of TTF and PFS on prognosis. In mRCC, it is important to use a highly effective drug at an early stage for as long as possible as the effect of tumor burden reduction in the early stage of sunitinib treatment affects subsequent prognosis [5]. Additionally, it has been reported that long-term treatment at a dose to achieve tumor burden reduction is associated with a favorable prognosis. Therefore, PFS associated with tumor growth and TTF associated with treatment continuation are considered to have a strong impact on the prognosis of mRCC. The prognostic factors of TTF and PFS may be important indicators for selecting a targeted agent for mRCC.

We found that hand-foot syndrome was a prognostic factor for PFS. Hand-foot syndrome has been reported to be a favorable prognostic factor for sunitinib [28]. Hand-foot syndrome is a dose-related AE. Therefore, in the absence of the development of hand-foot syndrome, an antitumor effect is not achieved, leading to tumor growth and may affect shorter PFS.

We found that high AST (>30 U/L) and ALP (>322 U/L) levels and 6-week RDI (<60%) were prognostic factors for TTF. High AST and ALP levels are associated with liver and bone metastases and indicate poor PS [7,29]. RDI <60% during the first 6 weeks of sunitinib is the initial dose for which an antitumor effect cannot be expected and has been associated with poor prognosis [30]. Therefore, poor PS and treatment with an initial dose of sunitinib that is not expected to have an antitumor effect may affect TTF.

We showed that the developed OS prognostic model accurately predicted the prognosis of patients with mRCC treated with sunitinib. This suggests that this model may be a clinical criterion for continuation of sunitinib treatment in patients with RCC who wish to survive longer. The low-risk group achieved an antitumor effect from the VEGFR inhibitor sunitinib, which is expected to lead to a longer OS. On the other hand, in the high-risk group, a longer OS cannot be expected even if sunitinib is selected, so it is necessary to consider changing to other molecular-targeted agents or immune checkpoint inhibitors.

We also showed that the developed prognostic models of TTF and PFS accurately predicted the prognosis of patients with mRCC treated with sunitinib. These results suggest that the models may be clinical criteria for continuation of sunitinib treatment in patients with RCC who wish to reduce the tumor burden or continue sunitinib treatment.

Limitations

The present study has two limitations. First, there were few patients treated with sunitinib as first-line therapy; therefore, a prognostic model could not be developed for patients with mRCC treated with sunitinib as first-line therapy. Second, a prognostic model that included the severity of AEs could not be developed.

Conclusions

We first demonstrated that the 6-week COP-NLR, which was associated with TTF, PFS, and OS, was an important prognostic factor in patients with mRCC treated with sunitinib. The developed prognostic model for OS, including the 6-week COP-NLR, will be useful in

decision-making to continue sunitinib in the early treatment stage of patients with mRCC. The low-risk group can achieve the antitumor effect of the VEGFR inhibitor sunitinib, which is expected to lead to longer OS.

Abbreviations

AEs
Adverse events
Alb
Albumin
ALP
Alkaline phosphatase
AST
Aminotransferase
COP-NLR
Combination of platelet count and neutrophil–lymphocyte ratio
CRP
C-reactive protein
CT
Computed tomography
HRs
Hazard ratios
LDH
Lactate dehydrogenase
mGPS
Modified glasgow prognostic score
mRCC
Metastatic renal cell carcinoma
MRI
Magnetic resonance imaging
MSKCC
Memorial sloan kettering cancer center
OS
Overall survival
PFS
Progression-free survival
PS
Performance status
RCC
Renal cell carcinoma
RDI
Relative dose intensity
RECIST
Response evaluation criteria in solid tumors
TTF
Time to treatment failure
VEGFR
Vascular endothelial growth factor receptor

Declarations

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Availability of data and materials

The datasets generated during and analyzed during the current study are not publicly available due to ethical reasons but are available from the corresponding author on reasonable request.

Authors' contributions

All authors contributed to the study conception and design. MTS, AI, YK and KT performed data collection and analysis. MTS, MO, NK, JM, KF, HS, YO and MK performed interpretation of the data. MTS wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Showa University School of Pharmacy, Japan (No. 366). This study was performed in line with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Patient characteristics

Characteristics (n = 102)	N	%	Characteristics	N	%
Patient characteristics			**RDI during the first 6 weeks of sunitinib**		
Sex			Median (range), %	62.5 (17.9-100)	
Male	83	81.4	Duration of therapy		
Age			Median (range), days	140 (5-2012)	
Median (range), years	67.5 (28-83)		**Laboratory data at start of sunitinib**		
ECOG-PS			AST		
0	64	62.7	≤30 U/L	83	81.4
1	23	22.6	>30 U/L	19	18.6
≥2	15	14.7	Alb		
Histology type			<3.5 g/dL	33	32.4
Clear cell	76	96.2	≥3.5 g/dL	69	67.6
Non-clear cell	3	3.8	CRP		
Prior nephrectomy	75	73.5	≤0.5 g/dL	44	43.1
Metastatic sites			>0.5 g/dL	58	56.9
Lung	69	67.6	ALP		
Bone	25	24.5	≤322 U/L	61	61.6
Lymph node	30	29.4	>322 U/L	38	38.4
Liver	15	14.7	mGPS		
Other	23	22.5	0	42	41.2
Number of metastatic sites			1	28	27.5
0	3	2.9	2	32	31.3
1	45	44.2	COP-NLR		
≥2	54	52.9	0	49	49
MSKCC risk group			1	36	36
Favorable	13	12.8	2	15	15
intermediate	70	68.6	**Laboratory data within the first 6 weeks of sunitinib**		
poor	19	18.6	Alb		
Treatment characteristics			<3.5 g/dL	51	51
Prior immunotherapy	21	20.6	≥3.5 g/dL	49	49
Prior targeted therapy	13	12.7	CRP		
Treatment			≤0.5 g/dL	26	25.7
1st line	75	73.5	>0.5 g/dL	75	74.3
2st line	18	17.7	LDH		
3st line	9	8.8	≤333 U/L	76	76
Initial dose			>333 U/L	24	24
50 mg	47	46	mGPS		

37.5 mg	42	41.2	0	24	24.2
25 mg	12	11.8	1	26	26.3
12.5 mg	1	1	2	49	49.5
Treatment schedule			COP-NLR		
4-week on / 2-week off	35	34.3	0	71	74
2-week on / 1-week off	64	62.7	1	22	22.9
Other	3	3	2	3	3.1

ECOG PS, Eastern Cooperative Oncology Group Performance Status; MSKCC, Memorial Sloan Kettering Cancer Center; RDI, Relative Dose Intensity; AST, aspartate aminotransferase; Alb, albumin; CRP, C-reactive protein; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; mGPS, modified Glasgow Prognostic Score; COP-NLR, combination of platelet count and neutrophil–lymphocyte ratio.

Table 2 Univariate and multivariate analyses of factors associated with time to treatment failure, progression-free-survival, and overall survival

Variables	Time to treatment failure				Progression-free-survival				Overall survival			
	Univariate		Multivariate[†]		Univariate		Multivariate[‡]		Univariate		Multivariate[§]	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Characteristics												
Sex (female vs male)	0.987	0.960			1.115	0.682			0.890	0.734		
Age (≥65 vs <65 years)	1.624	0.024			1.256	0.290			0.822	0.474		
ECOG PS (≥1 vs 0)	1.367	0.147			1.649	0.020			2.518	<0.001		
MSKCC risk group (poor vs others)	2.934	<0.001			3.340	<0.001	3.234	<0.001	9.115	<0.001	7.239	<0.001
Prior nephrectomy (yes vs no)	0.651	0.071			0.650	0.068			0.308	<0.001		
Number of metastatic sites (≥2 vs 0,1)	1.960	0.002	2.322	<0.001	2.369	<0.001	2.273	<0.001	2.756	0.001	3.260	0.001
6-week RDI (<60 vs ≥60%)	2.671	<0.001	3.160	<0.001	1.321	0.190			1.581	0.095		
Adverse events*												
Hypertension (yes vs no)	0.729	0.136			0.837	0.412			0.461	0.005	0.482	0.024
Hand-foot syndrome (yes vs no)	0.651	0.046			0.654	0.049	0.601	0.043	0.831	0.499		
Diarrhea (yes vs no)	1.497	0.080			1.487	0.087			1.776	0.047		
Hypothyroidism (yes vs no)	0.669	0.099			0.707	0.154			0.922	0.790		
Leukopenia (yes vs no)	1.201	0.389			1.537	0.047			1.421	0.206		
Thrombocytopenia (yes vs no)	0.792	0.350			1.062	0.814			0.606	0.112		
Elevation of ALP (yes vs no)	1.351	0.159			1.438	0.093			2.188	0.007		
Laboratory data at start of sunitinib												
AST (>30 vs ≤30 U/L)	2.160	0.003	2.303	0.009	2.060	0.006			2.689	0.002		
Alb (≥3.5 vs <3.5 g/dL)	0.550	0.008			0.469	0.001			0.225	<0.001		
CRP (>0.5 vs ≤0.5 g/dL)	2.239	<0.001			2.055	0.001			4.465	<0.001		
ALP (>322 vs ≤322 U/L)	2.102	<0.001	1.811	0.013	2.253	<0.001			3.134	<0.001		
mGPS (1, 2 vs 0)	2.037	0.001			2.134	<0.001			5.119	<0.001	2.946	0.005

COP-NLR (1, 2 vs 0)	1.271	0.256			1.327	0.184			2.823	0.001		
Laboratory data within the first 6 weeks of sunitinib												
Alb (≧3.5 vs <3.5 g/dL)	0.527	0.003			0.510	0.002			0.396	0.001		
CRP (>0.5 vs ≤0.5 g/dL)	1.732	0.026			1.718	0.034			1.421	0.286		
mGPS (1, 2 vs 0)	1.749	0.026			1.765	0.030			1.348	0.366		
COP-NLR (1, 2 vs 0)	2.898	0.001	2.255	0.003	2.799	0.001	2.270	0.004	4.357	0.001	2.860	0.002

**Adverse events were developed within the first 6 weeks of sunitinib. HR, Hazard ratio, ECOG PS, Eastern Cooperative Oncology Group Performance Status; MSKCC, Memorial Sloan Kettering Cancer Center; RDI, Relative Dose Intensity; AST, aspartate aminotransferase; Alb, albumin; CRP, C-reactive protein; ALP, alkaline phosphatase; mGPS, modified Glasgow Prognostic Score; COP-NLR, combination of platelet count and neutrophil– lymphocyte ratio.*
† Age, MSKCC risk group, number of metastatic sites, hand-foot syndrome, 6-week RDI, AST, ALP, mGPS, 6-week mGPS, and 6-week COP-NLR were subjected to multivariate analysis.
‡ MSKCC risk group, number of metastatic sites, hand-foot syndrome, leukopenia, mGPS, AST, ALP, 6-week mGPS, and 6-week COP-NLR were subjected to multivariate analysis.
§ MSKCC risk group, prior nephrectomy, number of metastatic sites, hypertension, diarrhea, elevation of ALP, AST, ALP, mGPS, COP-NLR, 6-week Alb, and 6-week COP-NLR were subjected to multivariate analysis.

Table 3 Treatment-related adverse events

Adverse events	All grades	(n, %)	Grade3-4	(n, %)
Hypertension	60	(58.8)	20	(19.6)
Hand-foot syndrome	49	(48.0)	7	(6.9)
Stomatitis	36	(35.3)	6	(5.9)
Dysgeusia	17	(16.7)	-	-
Oedema	14	(13.7)	0	(0)
Nausea / Vomiting	24	(23.5)	0	(0)
Hemorrhage	26	(25.5)	0	(0)
Constipation	16	(15.7)	0	(0)
Diarrhea	29	(28.4)	3	(2.9)
Fatigue	46	(45.1)	7	(6.9)
Hypothyroidism	26	(25.5)	5	(4.9)
Leukopenia	55	(53.9)	10	(9.8)
Thrombocytopenia	79	(77.5)	17	(16.7)
Anemia	70	(68.6)	5	(4.9)
Elevation of AST	63	(61.8)	8	(7.8)
Elevation of serum creatinine	53	(52.0)	5	(4.9)
Elevation of ALP	51	(51.5)	1	(1.0)

AST, aspartate aminotransferase; ALP, alkaline phosphatase.

Figures

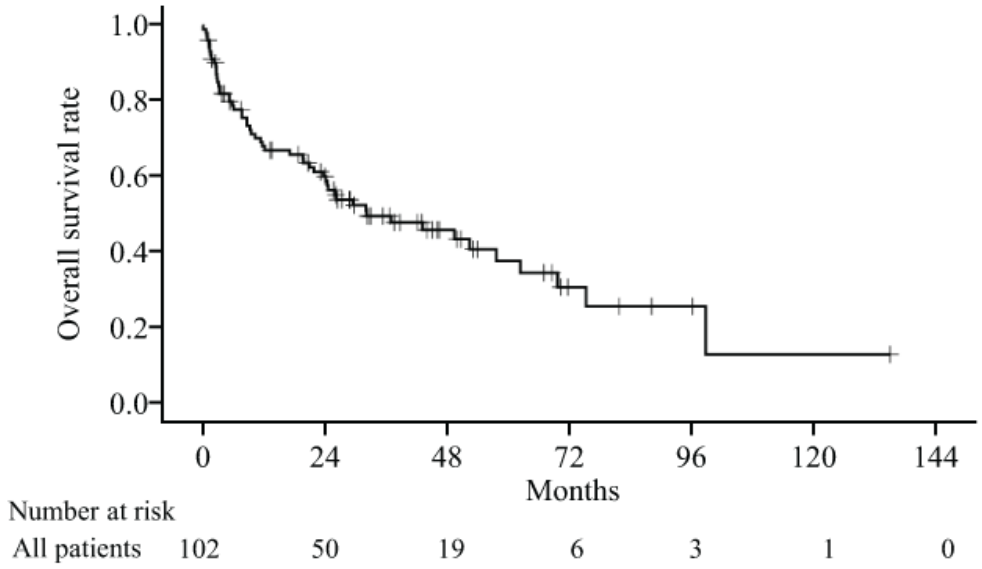

Figure 1

Cumulative survival curve of all patients

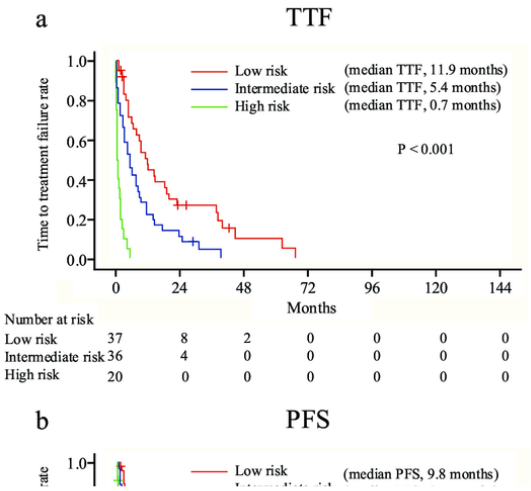

Figure 2

Kaplan–Meier curves of (A) time to treatment failure, (B) progression-free-survival, and (C) overall survival in the two groups divided according to the 6-week COP-NLR

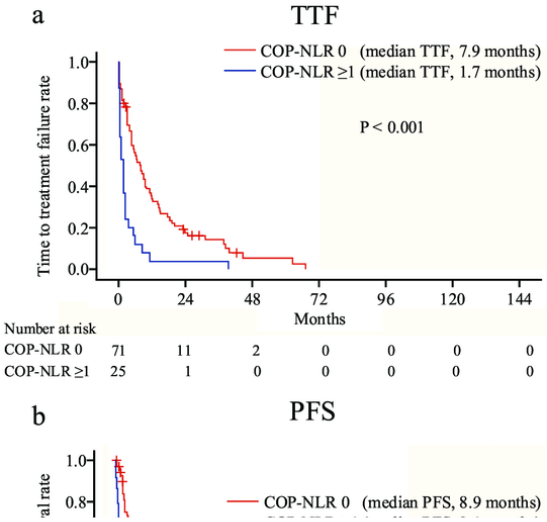

Figure 3

Kaplan–Meier curves of (A) time to treatment failure, (B) progression-free-survival, and (C) overall survival in the three groups divided according to the prognostic model