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ORIGINAL ARTICLE

Prognostic value of the Glasgow Prognostic Score for patients with metastatic renal cell carcinoma treated by cytoreductive nephrectomy

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Abstract

Background The aim of the present study was to evaluate the prognostic significance of the Glasgow Prognostic Score (GPS) in metastatic renal cell carcinoma (mRCC) patients treated by cytoreductive nephrectomy (CN), and the accuracy of the GPS as a prognostic factor.

Methods We retrospectively analyzed the data of patients who underwent CN for mRCC between March 1984 and August 2015. In accordance with the GPS criteria, the patients were classified into three groups: GPS 0: C-reactive protein (CRP) ≤ 1.0 mg/dl and albumin ≥ 3.5 g/dl; GPS 1: CRP > 1.0 mg/dl or albumin < 3.5 g/dl; and GPS 2: CRP > 1.0 mg/dl and albumin < 3.5 g/dl.

Results We enrolled 170 patients (72% male; median age 63.5 years). Fifty-six (33%), 67 (39%), and 47 (28%) patients had a GPS of 0, 1, and 2, respectively. The median overall survivals after CN were 52.4, 19.1, and 8.9 months for patients with a GPS of 0, 1, and 2, respectively ($P < 0.0001$). In addition to the GPS, Eastern Cooperative Oncology Group performance status (ECOG-PS), Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification, histology, sarcomatoid change, clinical T stage, primary tumor size, number of metastatic organs, non-regional lymph node metastasis, and liver metastasis were included in the Cox hazards regression model. Multivariate analysis of these factors revealed that the GPS was an independent prognostic factor of overall survival ($P < 0.0001$). Harrell's concordance index in the multivariate prognostic model based on ECOG-PS, MSKCC risk criteria, histology, sarcomatoid change, clinical T stage, primary tumor size, number of metastatic organs, non-regional lymph node metastasis, and liver metastasis was 0.609, which increased to 0.652 after the inclusion of the GPS.

Conclusions GPS represents an independent prognostic factor for patients who undergo CN for mRCC.

Keywords Prognosis · Glasgow Prognostic Score · Metastatic renal cell carcinoma · Cytoreductive nephrectomy · Overall survival

Introduction

Cytoreductive nephrectomy (CN) has been shown to result in survival benefits for patients with metastatic renal cell carcinoma (mRCC), as evaluated by two randomized trials and a combined analysis in the cytokine era [1–3]. In addition, some retrospective studies have shown similar survival benefits in the molecular-targeted drug era [4–7], although conflicting opinions exist [8].

These controversial results are currently being evaluated by two ongoing randomized trials (CARMENE and SURTIME). However, it is clear that not all patients with mRCC can receive survival benefits from CN. Thus, the indication for CN should be well-considered to avoid unnecessary invasive surgery. To optimize the benefits of CN, prognostic factors after CN, such as a high serum lactate dehydrogenase level [9–11], low albumin level [9, 11], symptoms of metastasis at presentation [9], elevated corrected calcium level [10], low performance status [10], and poor risk according

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to the Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification [12, 13] have been previously reported.

The Glasgow Prognostic Score (GPS) is a selective combination of the serum levels of C-reactive protein (CRP) and albumin, and is a simpler scoring system than most other prognostic models. This score has been shown to be an independent prognostic factor in a variety of cancers [14–16]. In the field of RCC, the GPS has been shown to be an independent prognostic factor in mRCC patients treated with cytokine therapy and in localized RCC patients undergoing potentially curative tumor resection [16, 17]. However, to the best of our knowledge, whether the GPS is also a prognostic factor for mRCC patients treated by CN has not been investigated.

With this in mind, in the present study we evaluated the prognostic significance of the GPS in patients with mRCC treated by CN, with the aim of optimizing the patient selection for CN.

Materials and methods

Patients

After approval by our institutional review board, the medical records of patients treated at our hospital, Tokyo Women's Medical University, were retrospectively reviewed and 170 patients with mRCC treated by CN between March 1984 and August 2015 were identified. The tumor stage was determined according to the 2009 TNM classification [18]. The pathological diagnoses were made according to the 2016 World Health Organization classification [19]. Stratification of prognostic risk was performed according to the MSKCC risk classification [20].

Measurements and definitions

Clinical, laboratory, and survival data were collected by reviewing the electronic medical records of the patients. Pathological data were obtained from nephrectomy specimens. All surgical specimens were processed according to standard pathological procedures, and all specimens were histologically confirmed to be RCC by an authorized pathologist (YN).

The GPS was calculated as previously described [14]. Briefly, patients with an elevated CRP concentration (>1.0 mg/dl) and a decreased albumin concentration (<3.5 g/dl) were assigned a score of 2. Patients with an elevated CRP concentration (>1.0 mg/dl) or a decreased albumin concentration (<3.5 g/dl) were assigned a score of 1, while patients with a CRP concentration of ≤1.0 mg/dl and an albumin concentration of ≥3.5 g/dl were assigned a score of 0 (Table 1). The serum CRP and albumin levels were routinely measured before surgery. The targeted molecular therapy (TMT) era was defined as the period from March 2008, when sorafenib was first introduced in Japan.

Table 1 Glasgow Prognostic Score (GPS) criteria

	Points
C-reactive protein ≤ 1.0 mg/dl and albumin ≥ 3.5 g/dl	0
C-reactive protein > 1.0 mg/dl or albumin < 3.5 g/dl	1
C-reactive protein > 1.0 mg/dl and albumin < 3.5 g/dl	2

Statistical analysis

The clinicopathological variables were compared between the different GPS groups using the χ^2 test or analysis of variance, as appropriate. Overall survival (OS) curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Survival analysis was performed using Cox proportional hazards models. Their predictive accuracy was evaluated using Harrell's concordance index (c-index) [21]. A difference was considered significant at $P < 0.05$. All statistical analyses were performed using JMP 11.0.0 (SAS Institute, Cary, NC, USA) and SAS v.9.4 (SAS Institute).

Results

Patient characteristics

Table 2 shows the characteristics of the 170 mRCC patients treated with CN. Because all patients had synchronous metastasis at the time of diagnosis of RCC, there were no patients defined as having favorable risk in the MSKCC risk classification. A total of 119 (70%) and 51 (30%) patients were classified as being at intermediate and poor risk, respectively. According to the GPS criteria, 56 (33%), 67 (39%), and 47 (28%) patients were categorized as GPS 0, GPS 1, and GPS 2, respectively. In addition, the treatments used for the metastases existing at the time of CN are described in Table 3.

Association between the GPS and survival

During the follow-up period, 108 patients (62%) died of various causes, including 99 patients (57%) due to RCC. Because the Kaplan–Meier curves for OS were stable after 100 months of follow-up (data not shown), Fig. 1 shows the survival data until 100 months after CN. As a result, a significant difference in the OS rates between patients with GPS 0 (median 52.4 months), GPS 1 (median 19.1 months), and GPS 2 (median 8.9 months) was observed ($P < 0.0001$).

Table 2 Patient characteristics ($N = 170$)

Age, years, median (95% confidence interval)	63.5 (61.4–64.5)
Sex, *n* (%)	
Male	122 (72)
Female	48 (28)
ECOG-PS, *n* (%)	
0	102 (60)
1	47 (28)
2	15 (9)
3	6 (3)
MSKCC risk, *n* (%)	
Intermediate	119 (70)
Poor	51 (30)
Histology, *n* (%)	
Clear cell carcinoma	156 (92)
Non-clear cell carcinoma	14 (8)
Sarcomatoid change, *n* (%)	23 (14)
GPS, *n* (%)	
0	56 (33)
1	67 (39)
2	47 (28)

ECOG-PS Eastern Cooperative Oncology Group performance status, *MSKCC* Memorial Sloan-Kettering Cancer Center, *GPS* Glasgow Prognostic Score

Table 3 Treatment for metastasis existing at cytoreductive nephrectomy

Targeted molecular therapy, *n* (%)	65 (38)
Sunitinib, *n* (%)	36 (21)
Sorafenib, *n* (%)	18 (11)
Temsirolimus, *n* (%)	4 (2)
Pazopanib, *n* (%)	5 (3)
Axitinib, *n* (%)	2 (1)
Other therapies, *n* (%)	105 (62)
Interferon, *n* (%)	63 (37)
IL-2, *n* (%)	5 (3)
Interferon + IL-2, *n* (%)	2 (1)
Metastasectomy, *n* (%)	9 (5)
EBRT, *n* (%)	6 (4)
None, *n* (%)	14 (8)
Unknown, *n* (%)	6 (4)

IL-2 interleukin-2, *EBRT* external beam radiation therapy

Differences in clinicopathological features between patients with GPS 0, GPS1, and GPS 2

Table 4 shows the differences in clinicopathological features between the patients with GPS 0, GPS 1, and GPS 2. The MSKCC risk ($P = 0.0006$), treatment for metastasis existing at the time of CN ($P = 0.02$), sarcomatoid change ($P = 0.0003$), primary tumor size ($P < 0.0001$), and lung metastasis ($P = 0.028$) significantly differed between the groups. Furthermore, the association between the GPS and another systemic inflammation marker, the neutrophil-to-lymphocyte ratio (NLR) [22], was investigated. We evaluated 152 patients who had complete data of both the GPS and NLR. As a result, the GPS was significantly associated with the NLR ($P < 0.0001$).

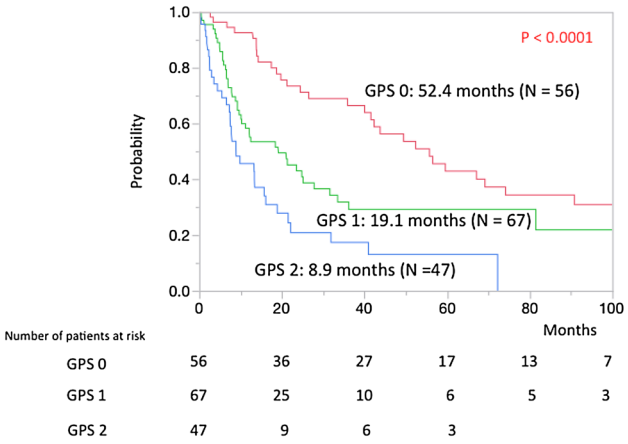

Fig. 1 Kaplan–Meier curves of overall survival according to the Glasgow Prognostic Score (GPS) in metastatic renal cell carcinoma patients treated by cytoreductive nephrectomy. The data after 100 months were eliminated

Relationships between clinicopathological factors and OS in mRCC patients treated with CN

Univariate analysis showed that Eastern Cooperative Oncology Group performance status (ECOG-PS) ($P = 0.0006$), MSKCC risk ($P < 0.0001$), histology ($P = 0.0077$), sarcomatoid change ($P = 0.0008$), clinical T stage ($P = 0.045$), primary tumor size ($P = 0.0091$), number of metastatic organs ($P = 0.012$), non-regional lymph node metastasis ($P = 0.048$), liver metastasis ($P = 0.0004$), and the GPS ($P < 0.0001$) were significantly associated with OS (Table 5). Multivariate analysis was performed using the factors significantly associated with OS in the univariate analysis, and revealed that the GPS was an independent prognostic factor for OS ($P < 0.0001$) (Table 6). Furthermore, the c-index was calculated to evaluate the predictive accuracy of the GPS. The c-index of the multivariate prognostic model based on the factors significantly associated with OS in the univariate analysis without GPS (ECOG-PS, MSKCC risk, histology, sarcomatoid change, clinical T stage, primary tumor size, number of metastatic organs, non-regional lymph node metastasis, and liver metastasis) was 0.609, and this value was further enhanced by the inclusion

Table 4 Patient and disease characteristics stratified according to the GPS

Characteristics	GPS 0 ($N = 56$)	GPS 1 ($N = 67$)	GPS 2 ($N = 47$)	P value
Age, years, median (95% CI)	62.5 (59.3–64.6)	64.0 (61.8–66.7)	64.0 (59.5–65.3)	0.42
Sex, *n* (%)				0.94
Male	40 (71)	49 (73)	33 (70)	
Female	16 (29)	18 (27)	14 (30)	
ECOG-PS, *n* (%)				0.27
0–1	51 (91)	60 (90)	38 (81)	
≥2	5 (9)	7 (10)	9 (19)	
MSKCC risk, *n* (%)				0.0006
Intermediate	48 (86)	47 (70)	24 (51)	
Poor	8 (14)	20 (30)	23 (49)	
Treatment for metastasis existing at CN, *n* (%)				0.02
TMT	14 (25)	27 (40)	24 (51)	
Other	42 (75)	40 (60)	23 (49)	
Histology, *n* (%)				0.33
Clear cell carcinoma	50 (89)	64 (96)	42 (89)	
Non-clear cell carcinoma	6 (11)	3 (4)	5 (11)	
Sarcomatoid change, *n* (%)	1 (2)	9 (13)	13 (28)	0.0003
Clinical T stage, *n* (%)				0.21
cT1–2	17 (30)	13 (19)	8 (17)	
cT3–4	39 (70)	54 (81)	39 (83)	
Clinical nodal stage, *n* (%)				0.33
N0	45 (80)	45 (67)	30 (64)	
N1	2 (4)	6 (9)	5 (11)	
N2	9 (16)	16 (24)	12 (25)	
Primary tumor size, mm, median (95% CI)	60.0 (58.3–73.9)	90.0 (87.4–101)	100 (88.1–105)	< 0.0001
Number of metastatic organs, *n* (%)				0.18
1	44 (79)	44 (66)	30 (64)	
≥2	12 (21)	23 (34)	17 (36)	
Metastatic sites				
Lung metastasis, *n* (%)	35 (63)	56 (84)	34 (72)	0.028
Adrenal metastasis, *n* (%)	2 (4)	2 (3)	4 (9)	0.38
Non-regional lymph node metastasis, *n* (%)	9 (16)	13 (19)	10 (21)	0.79
Pancreatic metastasis, *n* (%)	3 (5)	0 (0)	2 (4)	0.075
Bone metastasis, *n* (%)	15 (27)	12 (18)	14 (30)	0.29
Brain metastasis, *n* (%)	2 (4)	3 (4)	1 (2)	0.79
Liver metastasis, *n* (%)	1 (2)	7 (10)	6 (13)	0.05
Other, *n* (%)	3 (5)	7 (10)	1 (2)	0.17
NLR, median (95% CI)	2.31 (2.11–3.21)	3.19 (3.28–4.27)	3.96 (3.98–5.09)	< 0.0001

GPS Glasgow Prognostic Score, *CI* confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *MSKCC* Memorial Sloan-Kettering Cancer Center, *TMT* targeted molecular therapy, *NLR* neutrophil-to-lymphocyte ratio

of the GPS (c-index 0.652), as compared to inclusion of CRP alone (c-index 0.631) and albumin alone (c-index 0.649).

Prognostic impact of the GPS on mRCC patients treated without CN

It is not clear whether the GPS has prognostic value in mRCC patients treated without CN. Thus, we also assessed the prognostic value of the GPS in mRCC patients treated without CN. Twenty-seven mRCC patients treated without CN were analyzed for OS according to the GPS using Kaplan–Meier curves. As a result, higher GPS tended to be associated with a poor survival rate (median OS: GPS 0: 18 months; GPS 1: 10 months; GPS 2: 6 months), although the difference was not statistically significant (Fig. 2).

Table 5 Univariate analysis of prognostic factors for overall survival in metastatic renal cell carcinoma patients treated by cytoreductive nephrectomy

Univariate analysis	HR	95% CI	*P* value
Age	1.02	0.99–1.04	0.10
Sex			0.33
Male	1.00	Reference	
Female	1.24	0.80–1.86	
ECOG-PS			0.0006
0, 1	1.00	Reference	
≥2	2.71	1.57–4.41	
MSKCC risk			< 0.0001
Intermediate	1.00	Reference	
Poor	2.63	1.76–3.90	
Treatment for metastasis existing at CN			0.30
TMT	1.00	Reference	
Other	1.26	0.82–1.97	
Histology			0.0077
Clear cell carcinoma	1.00	Reference	
Non-clear cell carcinoma	2.83	1.35–5.34	
Sarcomatoid change	2.77	1.57–4.60	0.0008
Clinical T stage			0.045
cT1–2	1.00	Reference	
cT3–4	1.64	1.01–2.82	
Clinical nodal stage			0.098
N0	1.00	Reference	
N1	0.91	0.35–1.94	
N2	1.70	1.04–2.68	
Primary tumor size	1.01	1.00–1.01	0.0091
Number of metastatic organs			0.012
1	1.00	Reference	
≥2	1.73	1.13–2.59	
Lung metastasis	0.80	0.52–1.27	0.34
Adrenal metastasis	2.03	0.79–4.27	0.13
Non-regional lymph node metastasis	1.67	1.00–2.66	0.048
Pancreatic metastasis	1.32	0.32–3.51	0.65
Bone metastasis	1.14	0.70–1.78	0.59
Brain metastasis	1.52	0.46–3.63	0.45
Liver metastasis	4.32	2.05–8.24	0.0004
Other metastasis	1.07	0.45–2.14	0.87
GPS			< 0.0001
0	1.00	Reference	
1	2.12	1.31–3.47	
2	3.81	2.27–6.44	

HR hazard ratio, *CI* confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *MSKCC* Memorial Sloan-Kettering Cancer Center, *TMT* targeted molecular therapy, *GPS* Glasgow Prognostic Score

Table 6 Multivariate analysis of prognostic factors for overall survival in metastatic renal cell carcinoma patients treated by cytoreductive nephrectomy

Multivariate analysis	HR	95% CI	*P* value
ECOG-PS			0.0042
1–2	1.00	Reference	
3–4	2.47	1.35–4.36	
MSKCC risk			0.017
Intermediate	1.00	Reference	
Poor	1.85	1.12–3.01	
Histology			0.004
Clear cell carcinoma	1.00	Reference	
Non-clear cell carcinoma	3.50	1.53–7.32	
Sarcomatoid change	2.14	1.13–3.88	0.021
Clinical T stage			0.44
cT1–2	1.00	Reference	
cT3–4	1.25	0.72–2.27	
Primary tumor size	1.0001	0.99–1.01	0.75
Number of metastatic organs			0.31
1	1.00	Reference	
≥2	1.32	0.77–2.20	
Non-regional lymph node metastasis	1.13	0.59–2.11	0.70
Liver metastasis	3.88	1.74–7.97	0.0016
GPS			0.013
0	1.00	Reference	
1	2.19	1.26–3.83	
2	2.23	1.17–4.22	

HR hazard ratio, *CI* confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *MSKCC* Memorial Sloan-Kettering Cancer Center, *GPS* Glasgow Prognostic Score

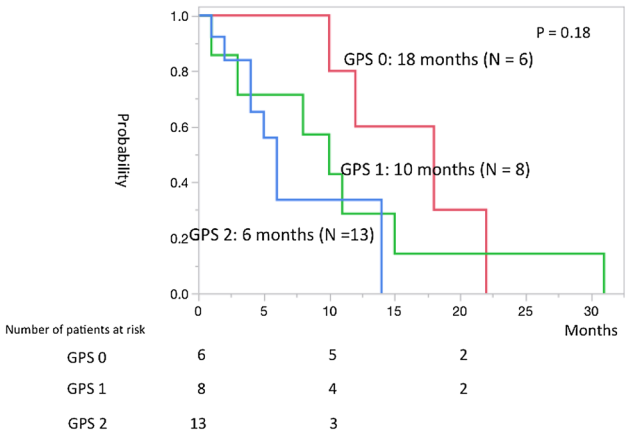

Fig. 2 Kaplan–Meier curves of overall survival according to the Glasgow Prognostic Score (GPS) in metastatic renal cell carcinoma patients treated without cytoreductive nephrectomy

Impact of CN on mRCC patients according to the GPS

Finally, we assessed the impact of CN on mRCC patients according to the GPS using Kaplan–Meier curves. Treatment by CN was associated with significantly better survival compared to treatment without CN in mRCC patients classified as GPS 0 and 1, whereas no association was seen in patients classified as GPS 2 (Fig. 3a–c).

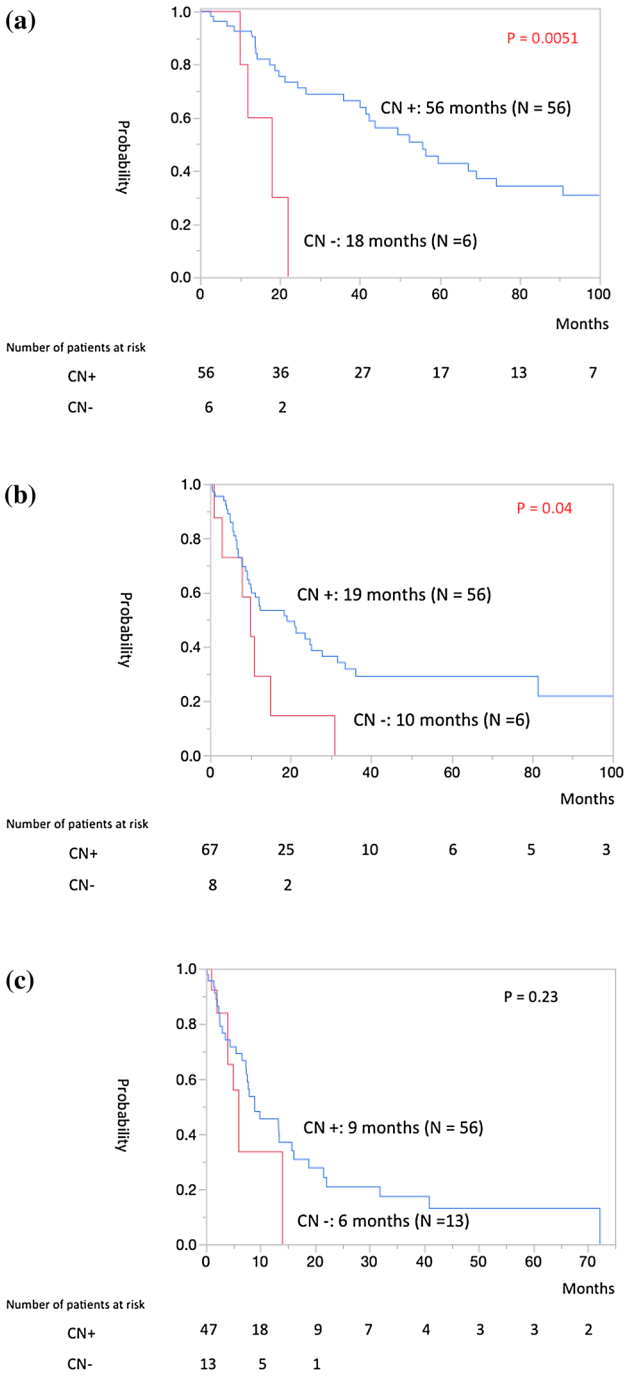

Fig. 3 Kaplan–Meier curves of overall survival in metastatic renal cell carcinoma patients who did or did not receive cytoreductive nephrectomy. **a** Glasgow Prognostic Score (GPS) of 0, **b** GPS 1, **c** GPS 2

Discussion

The present study showed that the GPS was an independent prognostic factor for OS in mRCC patients treated by CN, as determined using multivariate analysis, and that the addition of the GPS to the 9 prognostic factors (ECOG-PS, MSKCC risk, histology, sarcomatoid change, clinical T stage, primary tumor size, number of metastatic organs, non-regional lymph node metastasis, and liver metastasis) improved the predictive accuracy for OS (c-index 0.609 vs. 0.652).

Prognostic factors for mRCC have been investigated in clinical trials and retrospective multivariate analyses. Motzer et al. presented a prognostic model including low Karnofsky performance status, high lactate dehydrogenase, low serum hemoglobin, high corrected serum calcium, and time from initial RCC diagnosis to start of interferon therapy of less than 1 year, using data from the cytokine era [20]. This prognostic model was subsequently validated by Mekhali et al. [23]. In addition, Heng et al. presented the International Metastatic Renal-Cell Carcinoma Database Consortium model, which includes anemia, thrombocytosis, neutrophilia, hypercalcemia, Karnofsky performance status < 80%, and <1 year from diagnosis to treatment, in patients with mRCC treated with first-line vascular endothelial growth factor-targeted treatment [24]. Moreover, CRP and CRP kinetics have been reported as prognostic factors for survival in mRCC patients [25, 26]. However, the prognostic factors for mRCC patients treated by CN have not been sufficiently investigated.

The GPS is calculated based on a combination of the serum CRP and albumin levels and has been shown to be associated with the chronic inflammatory response [14]. This score has been validated as a prognostic marker in a variety of cancers [15]. RCC may induce a systemic inflammatory response, since it has been confirmed that several renal tumors can produce interleukin-6, a pro-inflammatory cytokine [27, 28], resulting in the production of CRP in the liver [29]. Moreover, albumin concentrations can reflect both systemic inflammation and the amount of lean tissue in patients with cancer [15, 30]. Thus, the GPS, a combination of CRP and albumin, has predictive potential in mRCC patients. Lamb et al. prospectively investigated the prognostic value of a modified GPS in 169 patients undergoing curative nephrectomy for clear cell cancer. They concluded that the modified GPS was at least equivalent to, and independent of, other current validated scoring systems [17].

However, as mentioned above, the prognostic value of the GPS has not been examined in mRCC patients undergoing CN thus far. Thus, the present study evaluated the

prognostic significance of the GPS in mRCC patients treated by CN and the accuracy of GPS as a prognostic factor. In previous studies, other systemic inflammatory prognostic factors have been examined. For example, the NLR has been reported to be a useful prognostic factor for mRCC patients in some studies [31, 32], and it was confirmed that the GPS was associated with the NLR in the present study (Table 4). Gu et al. indicated that the systemic inflammation response index, based on the pretreatment hemoglobin level and lymphocyte-to-monocyte ratio, was an independent prognostic predictor and was significantly correlated with the tumor behavior in mRCC patients treated by CN [33]. Moreover, Sakai et al. showed that the preoperative CRP level was independently associated with OS in mRCC patients who underwent CN and subsequently received immunotherapy and/or molecular-targeted therapy [34]. Similar to the previous studies for other systemic inflammatory prognostic factors, the prognostic value of the GPS was indicated in the present study using multivariate analysis and the c-index. The results of the present study suggest that the GPS is a potential biomarker and a potential candidate for constructing a nomogram for predicting outcome in mRCC patients treated by CN.

Although it has not been determined which mRCC patients can benefit from CN, one retrospective study aimed to determine the OS benefit of CN compared with no CN in mRCC patients treated with targeted therapies using data from 1658 mRCC patients from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) [5]. This study indicated that mRCC patients with four or more of the IMDC prognostic criteria did not benefit from CN. In the present study, a GPS of 2 (median OS 8.9 months) was associated with poor OS in mRCC patients treated with CN, as compared with a GPS of 0 or 1 (median OS 49.5 and 19.1 months, respectively). In addition, mRCC patients with GPS 0 and 1 benefitted from CN, whereas those with GPS 2 did not in our study (Fig. 3a–c). These results suggest that the GPS may also be useful for careful patient selection for CN.

There are some limitations in the present study, including its retrospective and single-center study design. In addition, we were not able to completely adjust for all potential confounding factors, owing to unknown or uncollected factors. Nevertheless, the present study indicates that the GPS may represent a useful prognostic factor for OS in mRCC patients treated by CN. Future large-scale, prospective, multi-center studies are warranted to confirm our findings.

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Compliance with ethical standards

Conflict of interest Tsunenori Kondo received remuneration for a lecture from Pfizer Japan (Tokyo, Japan) and Novartis Japan (Tokyo, Japan).

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