Lack of Association of Proteinuria and Clinical Outcome in Patients Treated with Bevacizumab for Metastatic Colorectal Cancer

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Abstract. *Background: Although bevacizumab-related hypertension has been reported as a predictive marker of therapy efficacy, an association between proteinuria and efficacy has not been reported. Patients and Methods: Eighty-two consecutive patients with metastatic colorectal cancer treated with bevacizumab as first-line treatment between July 2007 and April 2009 were examined. Results: Seventy-one patients were included in the analysis set. Proteinuria occurred in 29 patients: Grade 1 in 15 patients and grade 2 in 14 patients; no grade 3 or higher proteinuria was observed. The response rate did not increase with the severity of proteinuria (p=0.307). The median progression-free survival was 17.8 months in cases with grade 2 proteinuria, 16.0 months in those with grade 1 proteinuria, and 10.4 months in those with grade 0 proteinuria (p=0.030). In multivariate analysis with a time-dependent adjustment, there was no correlation between severity of proteinuria and survival. Conclusion: Bevacizumab-related proteinuria was not a predictive marker for patients with colorectal cancer treated with first-line bevacizumab.*

Bevacizumab is a humanized recombinant monoclonal antibody directed against vascular endothelial growth factor (VEGF) that inhibits VEGF-induced angiogenesis and tumor growth and may also reduce intratumoral pressure (1-3). The addition of bevacizumab to cytotoxic chemotherapy has been shown to provide clinical improvement in metastatic colorectal cancer (4-8).

Bevacizumab treatment is generally well-tolerated, but its use is associated with adverse vascular events, including an increased incidence of hypertension, proteinuria, thrombosis, and hemorrhage. Bevacizumab treatment has been associated with the development of proteinuria in 10-38% of patients with colorectal cancer, and in up to 71% of patients with renal cell carcinoma, of whom 7-15% experienced grade 3-4 proteinuria (4, 6, 9-12). Proteinuria is a well-known common side-effect of systemic inhibition of VEGF signaling, although the pathogenesis of VEGF signal inhibition-induced proteinuria is still not completely understood. One theory is that it is likely due to membranoproliferative glomerulonephritis (13). Glomerular endothelial repair may require VEGF and anti-VEGF therapy would thus interfere with glomerular endothelial integrity (14). In addition, erythropoietin stimulates VEGF release in the glomerulus and the low levels of erythropoietin in patients with cancer may aggravate proteinuria (15).

Recently, a case study of bevacizumab-related proteinuria and its clinical response was reported for breast cancer (16). However, few data exist on the impact of bevacizumab-related proteinuria as a biomarker. Therefore, we investigated the correlation between proteinuria and clinical outcome in a consecutive series of patients with metastatic colorectal cancer treated with bevacizumab as first-line treatment.

Patients and Methods

Patients. This was a retrospective study on patients with metastatic colorectal cancer who received bevacizumab as first-line therapy at the National Cancer Center Hospital, Tokyo from July 1, 2007 to April 30, 2009. Inclusion criteria for participation in this study were as follows: Histologically proven colorectal adenocarcinoma; unresectable advanced or recurrent disease; age less than 80 years; Eastern Cooperative Oncology Group performance status (PS) of 0

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or 1; no history of prior chemotherapy for advanced disease (adjuvant chemotherapy completed more than six months previously was allowed); adequate baseline bone marrow, hepatic, and renal functions (leucocyte count ≥3,000/mm^3, platelet count ≥100,000/mm^3, aspartate aminotransferase and alanine aminotransferase ≤100 U/l, total bilirubin ≤1.5 mg/dl, and serum creatinine ≤2.0 mg/dl); monitoring of the severity of proteinuria before and during treatment.

This study was approved by the Institutional Review Board of the National Cancer Center Hospital, and was conducted in compliance with the Ethical Guidelines for Epidemiological Research. This study is reported according to the STROBE statement (17).

Treatment. Bevacizumab was combined with modified FOLFOX-6 (oxaliplatin and fluorouracil/leucovorin), FOLFIRI (irinotecan and fluorouracil/leucovorin), or SIR (S-1 and irinotecan) which were administered at the physician's discretion or the patient's preference. Modified FOLFOX-6 plus bevacizumab consisted of a 120-min intravenous infusion of *l*-leucovorin at 100 mg/m^2, bolus infusion of fluorouracil at 400 mg/m^2, plus a 46-h intravenous infusion of fluorouracil at 2,400 mg/m^2, and a 120-min infusion of oxaliplatin at 85 mg/m^2 plus bevacizumab at 5 mg/kg every two weeks. FOLFIRI plus bevacizumab consisted of a 120-min intravenous infusion of l-leucovorin at 100 mg/m^2, bolus infusion of fluorouracil at 400 mg/m^2, plus a 46-h intravenous infusion of fluorouracil at 2,400 mg/m^2, and a 120-min infusion of irinotecan at 150 mg/m^2, plus bevacizumab 5 mg/kg every two weeks. SIR plus bevacizumab consisted of S-1 which was orally administered at 40 mg [body surface area (BSA) <1.25 m^2], 50 mg (BSA: 1.25-1.50 m^2), or 60 mg (BSA >1.50 m^2) twice a day for 14 days, followed by a one-week rest, irinotecan at 150 mg/m^2 on day 1, plus bevacizumab at 7.5 mg/kg on day 1 every three weeks. Treatment was continued until disease progression or unacceptable toxicity.

Study assessments. Urinary examination was performed bi-weekly or tri-weekly on day 1 of every cycle prior to chemotherapy. Proteinuria was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. The most severe grade of proteinuria was applicable to the analysis, and onset of proteinuria of any grade was recorded.

Outcome measures. The end-point of this study was the assessment of the correlation between proteinuria and tumor response, progression-free survival (PFS), and overall survival (OS). The response-to-treatment was assessed according to RECIST version 1.0 (18). PFS was defined as the interval between the start of bevacizumab-containing chemotherapy to clinical progression, or death, or last follow-up if no disease progression. OS was calculated from the start of bevacizumab-containing chemotherapy until the time of death or last follow-up.

Statistical analysis. We performed unadjusted and adjusted Cox proportional-hazards models to evaluate the association between proteinuria and PFS and OS during bevacizumab-containing chemotherapy. Models were adjusted for baseline performance status, primary site of disease, alkaline phosphatase (ALP) which was categorized into two groups: ≥300 and <300 U/l, and number of metastatic sites which were categorized into two groups: ≥2 and 1 using the Köhne prognostic index (19). Proteinuria was analyzed as a time-dependent covariate to minimize the bias between the time of exposure to bevacizumab and risk for proteinuria. Cases of early termination of bevacizumab therapy were excluded from the analysis set. Early termination was defined as bevacizumab therapy lasting less than four cycles for whatever reason.

We performed a Fisher's exact test to evaluate the association between proteinuria during bevacizumab-containing chemotherapy and the overall response. All confidence intervals (CI) and *p*-values in the Cox proportional-hazards models were determined with the use of the Wald chi-square test.

Median values, ranges, and proportions were used to describe baseline characteristics of the study population and to compare across all proteinuria grades. Median values and proportions were compared using the Wilcoxon rank-sum test and the Fisher's exact test, respectively.

The cumulative incidence of proteinuria was calculated with the use of the usual Kaplan–Meier estimator.

The median follow-up time was calculated by using the reverse Kaplan–Meier method (20). Survival curves were estimated using the Kaplan–Meier method, and differences were evaluated with the log-rank test. The confidence intervals of median survival time were calculated by the Greenwood formula.

All descriptive statistical analyses were performed with the use of the SAS software (version 9.2; SAS Institute, Inc., Cary, NC, USA). The Cox proportional-hazards models were performed with the PHREG procedure. Analyses with time-dependent covariates were performed using programming statements with the PHREG procedure. The proportions for categorical variables were calculated with the FREQ procedure. The summary statistics and Wilcoxon rank-sum test for continuous variables were calculated with the SUMMARY and NPAR1WAY procedure, respectively. The Kaplan–Meier estimates and the median survival estimates were calculated with the LIFETEST procedure. All statistical tests were two-sided, and significance was set at $p<0.05$, and 95% confidence intervals were calculated.

Results

Patients and analysis set. A total of 81 patients, who met the inclusion criteria, were identified, except for one patient who had not been monitored for proteinuria during treatment. Ten patients who had early termination of bevacizumab therapy were excluded from the analysis set. The reasons for exclusion were as follows: Disease progression (n=2), patient refusal (n=3), bevacizumab-related serious adverse thromboembolic event (n=2), and lost to follow-up (n=3). Therefore, 71 patients were included in the analysis set.

These patients' demographics and disease characteristics are presented in Table I. Subgroups of patients who had grade 1 or 2 proteinuria included more patients with poor PS compared to those of the grade 0 proteinuria group. The numbers of patients who had abnormal urinary qualitative examination before treatment were also significantly different between each grade group.

Proteinuria. The median follow-up time was 31.2 (range=5.4 to 43.3) months. As of the data collection cut-off date (April 30, 2011) for this analysis, proteinuria had occurred in 29

Table I. *Patients' characteristics*.

Characteristic	Patients with grade 0 proteinuria (n=42)		Patients with grade 1 proteinuria (n=15)		Patients with grade 2 proteinuria (n=14)		*p*-Value
Median age, years (range)	56	(28-76)	61	(40-76)	61.5	(46-72)	0.27
Gender, n (%)							0.51
Male	22	(52)	8	(53)	10	(71)	
Female	20	(48)	7	(47)	4	(29)	
Performance status, n (%)							0.01
0	31	(74)	5	(33)	7	(50)	
1	11	(26)	10	(67)	7	(50)	
Primary site, n (%)							0.72
Colon	25	(60)	7	(47)	8	(57)	
Rectum	17	(40)	8	(53)	6	(43)	
Disease, n (%)							0.74
Advanced	26	(62)	11	(73)	9	(64)	
Recurrence	16	(38)	4	(27)	5	(36)	
Adjuvant chemotherapy, n (%)							0.55
Yes	7	(17)	3	(20)	4	(29)	
No	35	(83)	12	(80)	10	(71)	
ALP, n (%)							0.69
≥300	15	(36)	5	(33)	3	(21)	
<300	27	(64)	10	(67)	11	(79)	
WBC, n (%)							1.00
≥10000	1	(2)	0	(0)	0	(0)	
<10000	41	(98)	15	(100)	14	(100)	
No. of metastatic sites, n (%)							0.88
1	14	(33)	4	(27)	5	(36)	
≥2	28	(67)	11	(73)	9	(64)	
Proteinuria before treatment[a], n (%)							<0.01
−	42	(100)	11	(73)	11	(79)	
±	0	(0)	2	(13)	2	(14)	
1+	0	(0)	2	(13)	1	(7)	
First-line chemotherapy, n (%)							0.49
FOLFOX with bevacizumab	32	(76)	9	(60)	9	(64)	
FOLFIRI with bevacizumab	2	(5)	1	(7)	0	(0)	
S-1/CPT with bevacizumab	8	(19)	5	(33)	5	(36)	

ALP, Alkaline phosphatase; WBC, white blood cells; FOLFOX, fluorouracil plus leucovorin and oxaliplatin; FOLFIRI, fluorouracil plus leucovorin and irinotecan; CPT, irinotecan. [a]Proteinuria was checked by urinary qualitative test (−, ±, 1+, 2+, 3+, or 4+).

patients (41%). The most severe grades of proteinuria were grade 1 in 15 patients (21%), and grade 2 in 14 patients (20%), while grade 3 or higher was not observed. Among the patients who experienced proteinuria, the median time-to-onset of the most severe grade was 5.3 (range=0.3 to 24.6) months. The median time to onset of the most severe grade 1 and grade 2 proteinuria was 7.3 (range=0.5 to 24.6) months and 3.5 (range=0.3 to 19.2) months, respectively (Figure 1).

Treatment and efficacy. The median number of cycles of bevacizumab in all populations, grade 0, grade 1, and grade 2 proteinuria groups were 18 (range=5 to >66), 19 (range=5 to >51), 26 (range=8 to >66), and 16 (range=5 to >53), respectively.

Out of the 69 evaluable patients, no patient had complete response, 44 patients (63.8%) showed partial response, 22 patients (31.9%) achieved stable disease without confirmation, and three patients (4.3%) had disease progression. For the entire study population, the median PFS was 12.7 months (95% CI=9.5 to 15.8 months), while the median OS was 34.6 months (95% CI=27.2 to 42.0 months).

The overall response was 78.6% in the grade 2 proteinuria group and 73.3% in the grade 1 proteinuria group, compared to 55.0% in the grade 0 proteinuria group (p=0.307) (Table II). The grade 2 and the grade 1 proteinuria groups had median PFS of 17.8 months (95% CI=10.9 to 21.7 months) and 16.0 months (95% CI=8.5 to 21.2 months), respectively, compared to that of the grade 0 group of 10.4 months (95% CI=9.3 to 13.4 months) (p=0.030) (Figure 2). The median overall survival was not also significantly different between each group (grade 2: 38.5 months, grade 1: not reached, and grade 0: 28.1 months, p=0.575) (Figure 3).

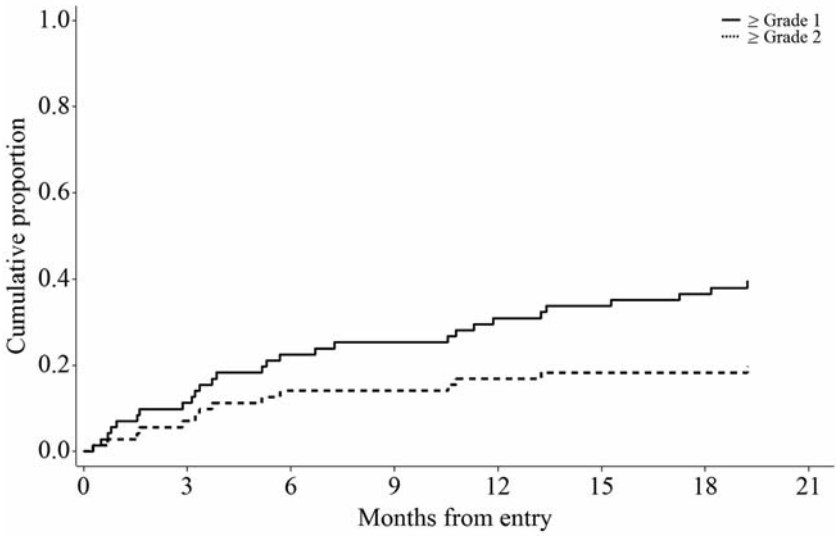

Figure 1. *Time of onset of proteinuria after bevacizumab therapy.*

Table II. *Efficacy results.*

	Patients with grade 0 proteinuria (n=42)		Patients with grade 1 proteinuria (n=15)		Patients with grade 2 proteinuria (n=14)		*p*-Value
Response rate [n (%)]	22	(55)	11	(73)	11	(79)	0.307[a]
CR [n (%)]	0	(0)	0	(0)	0	(0)	
PR [n (%)]	22	(55)	11	(73)	11	(79)	
SD [n (%)]	17	(43)	3	(20)	2	(14)	
PD [n (%)]	1	(3)	1	(7)	1	(7)	
NE [n (%)]	2	(4)	0	(0)	0	(0)	
Median OS [month (95% CI)]	28.1	(17.4)	.	(15.1)	38.5	(20.8)	0.58[b]
Median PFS [month (95% CI)]	10.4	(9.3-13.4)	16.0	(8.5-21.2)	17.8	(10.9-21.7)	0.030[b]

[a]Fisher's exact test; [b]Log-rank test. CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; OS, overall survival; PFS, progression-free survival; CI, confidence interval.

Survival analyses with a time-dependent adjustment for proteinuria. Table III shows the results of univariate and multivariate analyses of PFS and OS with Cox proportional hazards models with a time-dependent adjustment for proteinuria. Proteinuria was not a predictive marker, although ALP was an independent predictive marker for PFS (hazard ratio, HR=1.767, p=0.043). ALP (HR=2.297, p=0.025) and PS (HR=2.264, p=0.030) were independent predictive markers for OS.

Discussion

This study showed a relationship between the development of proteinuria during bevacizumab-containing therapy and improvements in PFS without a time-dependent covariate, but no significant relationship after the introduction/inclusion of a time-dependent covariate.

The addition of bevacizumab has been demonstrated to be more effective than previous standard treatment in many types of cancer (4, 5, 7, 10, 21-25). Nevertheless, few predictive factors have been identified with the efficacy of the VEGF signal inhibitor (26). Recently, patients who developed VEGF signal inhibitor-related hypertension after treatment with sunitinib, axitinib, or bevacizumab were reported to have longer OS than those who did not develop hypertension (27-29). However, there was no consensus as to which blood pressure levels should be recorded as hypertension. The clearest consensus was on the necessity of monitoring blood pressure levels carefully in patients

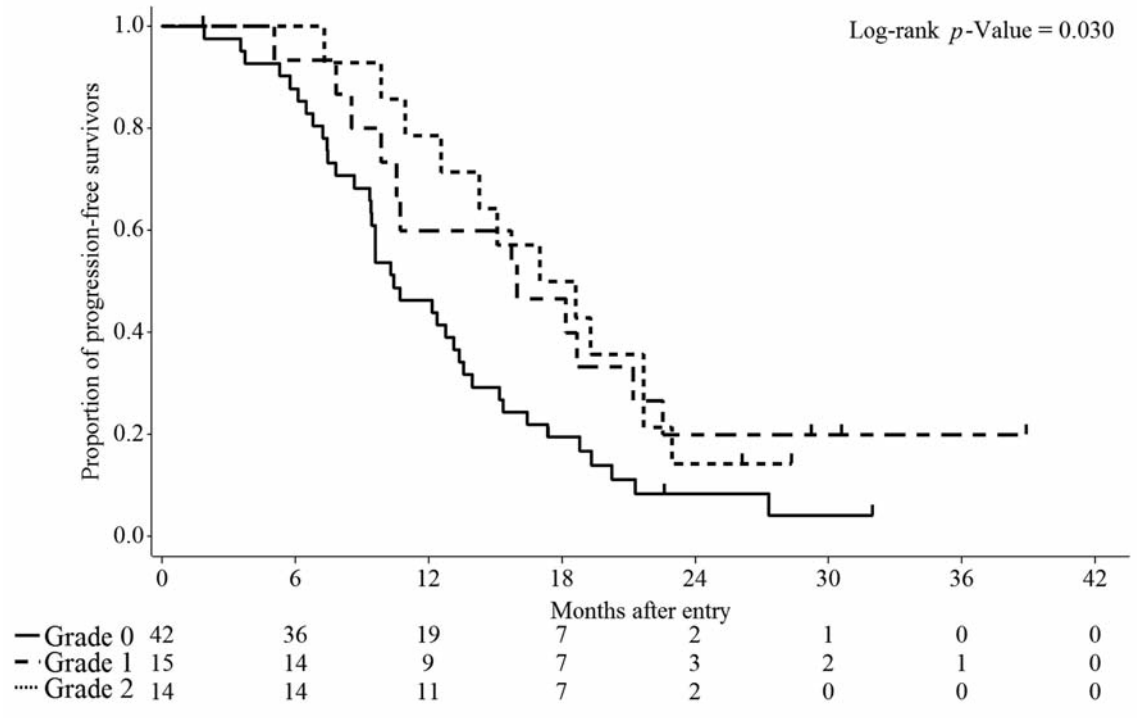

Figure 2. *Kaplan–Meier estimates of progression-free survival for patients with grade 0-2 proteinuria.*

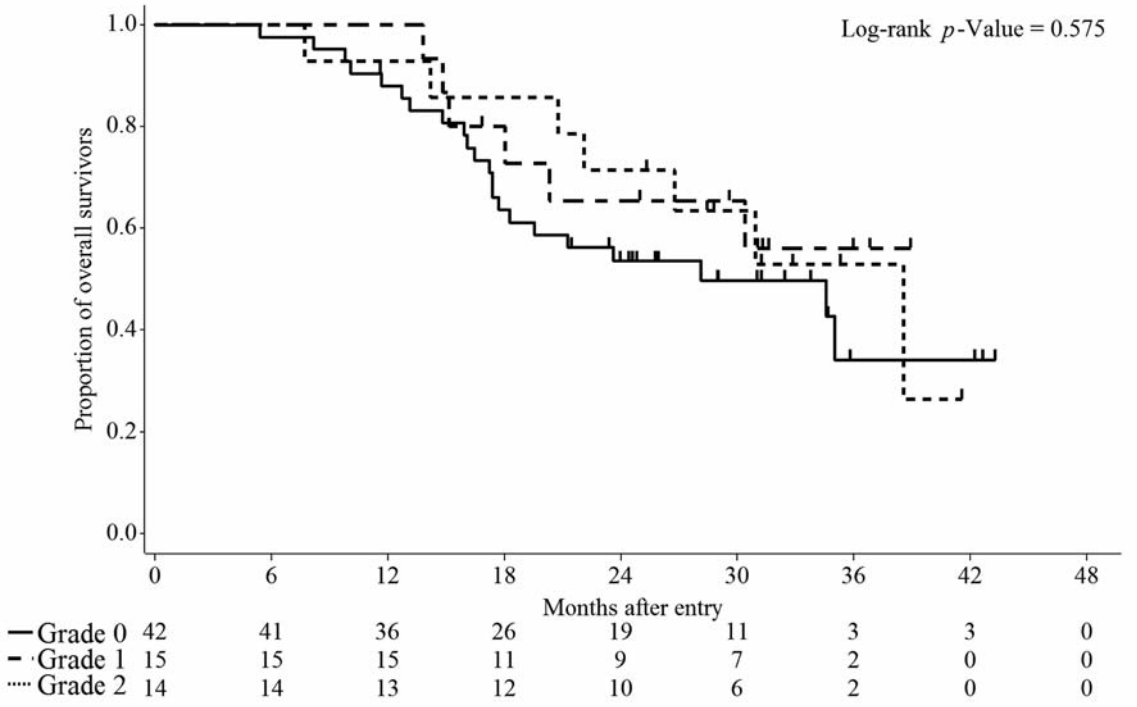

Figure 3. *Kaplan–Meier estimates of overall survival for patients with grade 0-2 proteinuria.*

Table IIIA. *Univariate and multivariate analysis for progression-free survival with Cox proportional hazards models with a time-dependent covariate.*

Variable *vs*. reference	Univariate analysis (n=71)	*p*-Value[a]	Multivariate analysis (n=71)	*p*-Value[a]
	Hazard ratio (95% CI[a])		Hazard ratio (95% CI[a])	
Proteinuria[b]				
Grade 1 *vs*. grade 0	1.199 (0.612 to 2.347)	0.596	1.187 (0.563 to 2.505)	0.652
Grade 2 *vs*. grade 0	0.854 (0.440 to 1.659)	0.642	0.869 (0.437 to 1.725)	0.687
PS				
1 *vs*. 0	0.940 (0.556 to 1.591)	0.819	0.944 (0.537 to 1.661)	0.842
Primary site of disease				
Rectum *vs*. colon	0.762 (0.457 to 1.269)	0.296	0.808 (0.468 to 1.394)	0.443
ALP (U/l)				
≥300 *vs*. <300	1.888 (1.113 to 3.201)	0.018	1.767 (1.019 to 3.066)	0.043
No. of metastatic sites				
≥2 *vs*. 1	1.104 (0.647 to 1.883)	0.717	1.081 (0.622 to 1.880)	0.782

Table IIIB. *Univariate and multivariate analysis for overall survival with Cox proportional hazards models with a time-dependent covariate.*

Variable *vs*. reference	Univariate analysis (n=71)	*p*-Value[a]	Multivariate analysis (n=71)	*p*-Value[a]
	Hazard ratio (95% CI[a])		Hazard ratio (95% CI[a])	
Proteinuria[b]				
Grade 1 *vs*. grade 0	0.902 (0.362 to 2.243)	0.824	0.565 (0.203 to 1.575)	0.275
Grade 2 *vs*. grade 0	0.897 (0.380 to 2.117)	0.803	0.714 (0.290 to 1.757)	0.463
PS				
1 *vs*. 0	1.945 (0.999 to 3.785)	0.050	2.264 (1.081 to 4.742)	0.030
Primary site of disease				
Rectum *vs*. colon	0.719 (0.365 to 1.415)	0.339	1.077 (0.507 to 2.286)	0.848
ALP (U/l)				
≥300 *vs*. <300	2.142 (1.088 to 4.218)	0.028	2.297 (1.108 to 4.761)	0.025
No. of metastatic sites				
≥2 *vs*. 1	2.072 (0.921 to 4.660)	0.078	2.083 (0.887 to 4.895)	0.092

[a]95% Confidence intervals (CI) and *p*-values were derived by the Wald chi-square test; [b]proteinuria was treated as a time-dependent covariate. PS: performance status; ALP: alkaline phosphatase.

receiving bevacizumab. Measuring proteinuria is an attractive biomarker strategy, as it is cheap and easily accessible. The causal relationship between hypertension, proteinuria and angiogenesis inhibitor introduction and their regression upon withholding the treatment would be coincidental to an initial decrease in nitric oxide expression followed by a resumption of its normal level of production. According to evidence from *in vitro* and *in vivo* studies showing that altered glomerular permeability appears to be an inhibitor of VEGF, proteinuria may indeed correlate with efficacy of bevacizumab therapy (4). Karachaliou *et al*. reported that bevacizumab-related proteinuria was associated with a favorable clinical outcome in a patient with metastatic breast cancer (16). However, Zee *et al*. found that the development of proteinuria during anti-VEGF therapy tended to be associated with poorer survival in patients with metastatic colorectal cancer (30). Therefore, it remained unknown whether the development of proteinuria might serve as a surrogate marker of antitumor efficacy. On the basis of this background, we focused on investigating the correlation between proteinuria and clinical outcome in patients with metastatic colorectal cancer treated with bevacizumab.

Our study has several limitations. Firstly, it might be possible that the duration of chemotherapy itself affects the development of proteinuria. We therefore analyzed proteinuria as a time-dependent covariate in order to minimize the bias between the exposure time to bevacizumab and risk for proteinuria. Secondly, the study's retrospective design may increase information bias. In an attempt to minimize this bias, we included consecutive patients who underwent first-line bevacizumab-containing chemotherapy. Several patients had incomplete urinary data at every visit. Thirdly, although OS is especially affected by subsequent chemotherapy, our study did not provide this information. Finally, severe bevacizumab-related proteinuria included a

relatively limited number of patients in a single center. Although we did not detect a difference in clinical outcome between different grades, our study might be underpowered to detect significant differences.

In conclusion, our study did not demonstrate that bevacizumab-related proteinuria was a surrogate marker of clinical outcomes in patients with metastatic colorectal cancer receiving a first-line bevacizumab-containing regimen.

Conflicts of interest

The Authors have declared no conflicts of interest.

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