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Risk Factors for Early Onset of Proteinuria in Patients Receiving Atezolizumab Plus Bevacizumab for Unresectable Hepatocellular Carcinoma

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Keywords
Hepatocellular carcinoma · Atezolizumab plus bevacizumab · Adverse events · Proteinuria · Vascular endothelial growth factor

Abstract

Introduction: Proteinuria is one of the adverse events of atezolizumab plus bevacizumab combination therapy (Atezo + Bev) and can cause interruption in the use of Bev. However, the risk factors for proteinuria in patients with hepatocellular carcinoma (HCC) who are receiving Atezo + Bev have not yet been investigated. The aim of this study was to identify the risk factors for early onset of proteinuria in Atezo + Bev for patients with unresectable HCC. ***Methods:*** Sixty-four patients with Child-Pugh scores of 5–7, an Eastern Cooperative Oncology Group performance status of 0 or 1, and low level of proteinuria (1+ or less on a dipstick test and urine protein-to-creatinine ratio (UPCR) less than 2.0 g/g Cr) at the initiation of therapy were analyzed. The level of proteinuria was evaluated based on the Common Terminology Criteria for Adverse Events version 5.0. We adopted the UPCR for the quantitative test instead of a 24-h urine collection. The incidence of proteinuria and changes in liver function were retrospectively investigated. ***Results:*** The cumulative incidence of proteinuria over a 24-week period was 34.4%. Multivariate analysis showed that a low estimated glomerular filtration rate (hazard ratio [HR], 3.807; 95% confidence interval [CI], 1.579–9.180; $p = 0.003$), treatment for hypertension (HR, 6.224; 95% CI, 1.614–24.010; $p = 0.008$), and high systolic blood pressure (SBP) (HR, 2.649; 95% CI, 1.133–6.194; $p = 0.025$) were risk factors for proteinuria. Serum albumin levels and albumin-bilirubin scores in patients with proteinuria worsened. In addition, a mean SBP ≥135 mm Hg during treatment was the only risk factor for the development of severe proteinuria (UPCR >2 g/g Cr). ***Conclusion:*** Our study found that controlling blood pressure is extremely important for the management of proteinuria in patients with HCC who are receiving Atezo + Bev.

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide [1]. HCC occurs commonly in patients with chronic hepatitis or

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liver cirrhosis secondary to either hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, excessive alcohol intake, nonalcoholic steatohepatitis, or diabetes [2]. While the development of antiviral therapy has resulted in a relative decrease in the occurrence of HCC due to HBV and HCV infections, an increase in patients with non-B-non-C-related HCC in patients with nonalcoholic steatohepatitis and metabolic syndrome has become a problem [3, 4].

Atezolizumab plus bevacizumab (Atezo + Bev) combination therapy was approved in 2020 as the first combined immunotherapy for HCC. Atezolizumab is a humanized monoclonal antibody to programmed cell death ligand 1. It blocks the binding of programmed cell death ligand 1 to PD-1 and thereby boosts anticancer immunity [5]. Bevacizumab targets vascular endothelial growth factor (VEGF), which stimulates angiogenesis and the growth of tumors [6, 7].

The IMbrave150 trial found that Atezo + Bev resulted in longer maintenance of the quality of life and better survival benefits than sorafenib [8]. The results of that trial suggest that Atezo + Bev should be a useful systemic therapy for HCC and should be used as a first-line treatment [9, 10]. However, proteinuria is known to be a major adverse event (AE) of Atezo + Bev for patients with HCC. Indeed, the incidence of proteinuria in the IMbrave150 trial was 20.1% [8].

In real-world practice, proteinuria associated with Atezo + Bev has occurred frequently and has been a major cause of interruption in the use of Bev [11, 12]. Negative consequences regarding antitumor efficacy when Bev treatment was interrupted early during the treatment of patients with HCC have also been reported [12]. Thus, the management of proteinuria in patients with HCC is important for maximizing the therapeutic effects of Atezo + Bev.

Patients treated with bevacizumab are monitored regularly for proteinuria by a dipstick test of a urine sample. The current standard for the management of patients treated with bevacizumab requires a 24-h urine protein test for a dipstick test result of ≥2+ proteinuria, with the further recommendation that bevacizumab treatment should be interrupted for a protein level of ≥2 g/24 h.

The 24-h urine protein test requires an overnight collection of urine by the patient, which is burdensome. The results also are affected by patient compliance. However, a urine protein-to-creatinine ratio (UPCR, g/g Cr) <2.0 g/g in a single-void urine sample is known to correlate significantly with 24-h proteinuria [13, 14]. Hence, in clinical practice, we often adopt the UPCR instead of the quantification of protein in a 24-h urine collection as an assessment of the degree of proteinuria.

Predictive factors for proteinuria in patients receiving Bev for several cancers have already been reported [15, 16]. However, the risk factors for proteinuria associated with anti-VEGF treatment for patients with HCC have not yet been investigated. Therefore, this retrospective study focused on identifying the risk factors for early onset of proteinuria in patients with unresectable HCC being treated by Atezo + Bev.

Materials and Methods

Patients

This retrospective cohort study included 87 patients treated with Atezo + Bev for unresectable HCC at our hospital from September 2020 to October 2021. We examined their records and collected their clinical data obtained during the treatment period. Patients positive for anti-HCV antibodies were considered to have HCC associated with HCV infection, while those positive for HBV surface antigen were considered to have HCC associated with HBV infection. Other patients were considered to have non-B, non-C hepatitis associated with HCC. 23 patients who had poor liver function or high-level proteinuria at baseline were excluded. Finally, a total of 64 patients with Child-Pugh scores ranging from 5 to 7, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and low-level proteinuria (1 + or less on the dipstick test and a UPCR <2.0 g/g Cr) at the initiation of therapy were analyzed.

Treatment Regimen

Patients received 1,200 mg of Atezo plus 15 mg per kg of body weight of Bev intravenously every 3 weeks. Interruptions to treatment and dose modifications were permitted for adverse drug reactions and the patient's general condition. Patients continued the therapy until death, or one of the following criteria was met for the cessation of therapy: progressive disease following treatments, AEs that required termination of treatment, increase in ECOG PS to 4, worsening liver function, or withdrawal of consent. Bev treatment was interrupted for a UPCR of ≥2.0 g/g Cr and was restarted when the UPCR decreased to <2.0 g/g Cr.

Assessment of Treatment Outcome

The evaluation used by imaging was performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guideline [17] with computed tomography and magnetic resonance imaging. Overall survival was defined as the time from initiation until death from any cause. Progression-free survival was defined as the period from initiation until the time of radiological progression by RECIST or any cause of death.

Blood Pressure

Systolic and diastolic blood pressures (SBPs and DBPs) were recorded between 9 a.m. and 10 a.m. when a study patient visited our hospital. The presence of hypertension in a study patient was

Table 1. Clinical background at initiation of Atezo + Bev combination therapy

Age, range, years	70 (47–90)	HbA1c (%), range	5.8 (4.1–8.8)
Sex (males/females), *n*	48/16	Proteinuria at baseline (– or ±/+1), *n*	51/13
Etiology (HBV/HCV/non-B non-C), *n*	10/26/28	UPCR (g/g Cre), range	0.16 (0.01–1.25)
Child-Pugh score (5/6/7), *n*	37/20/7	ECOG performance status (0/1), *n*	60/4
mALBI grade (1/2a/2b), *n*	24/17/23	BCLC stage (A/B/C), *n*	1/31/32
Serum BUN level (mg/dL), range	16.0 (8.1–57.7)	Macrovascular invasion (with/without), *n*	17/47
Serum creatinine lever (mg/dL), range	0.83 (0.45–2.06)	Extrahepatic metastasis (with/without), *n*	23/41
eGFR (mL/min/1.73 m^2), range	67 (25–137)	Serum AFP level (ng/mL), range	61.4 (1.4–35780)
Treatment for hypertension (with/without), *n*	41/23	Serum DCP level (mAU/mL), range	357.5 (15–201200)
Ca blocker (with/without), *n*	38/3	History of MTAs (with/without), *n*	29/35
ACE-I or ARB (with/without), *n*	19/22	Number of treatment cycles	6 (2–17)
α or β blocker (with/without), *n*	8/33	Observation period (months), range	8.1 (2.8–14.0)

HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI, albumin-bilirubin; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ACE-I, angiotensin-converting enzyme-inhibitor; ARB, angiotensin Ⅱ receptor blocker; UPCR, urinary protein-to-creatinine ratio; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; MTA, molecular targeted agent.

assessed by a recorded prescription for an antihypertensive (aHT) agent. The mean SBP/DBP during treatment was calculated as follows: mean SBP/DBP = the sum of SBPs/DBPs measured before every treatment divided by the number of treatments.

Proteinuria

Proteinuria was defined according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. A urine dipstick test and UPCR were performed at baseline and at every regular visit. UPCR was used as the quantitative test instead of a 24-h urine collection. Severe proteinuria was defined as a UPCR >2 g/g Cr.

Liver Function

The albumin-bilirubin (ALBI) score was used for liver function. The ALBI score was determined from laboratory test results for albumin and total bilirubin, where available. The following equation was used: ALBI score = ($\log_{10}$ bilirubin (μmoL/L) × 0.66) + (albumin (g/L) × −0.085) [18]. Modified ALBI (mALBI) grades were assigned according to the ALBI scores as follows: ALBI score ≤−2.60 was grade 1, −2.60< ALBI score ≤−2.27 was grade 2a, −2.27< ALBI score ≤−1.39 was grade 2 b, and ALBI score >−1.39 was grade 3 [19].

Statistical Analysis

Statistical analyses were performed using EZR ver. 1.53 software [20]. Normality for continuous variables was examined using the Kolmogorov-Smirnov test. The paired *T* test was used to compare between normally distributed continuous variables, and the Mann-Whitney test was used to compare non-normally distributed continuous variables. The Kaplan-Meier method was used to determine cumulative incidence. The log-rank test and Cox proportional hazard regression were used for univariate and multivariate analysis, respectively. Correlation analysis was performed using Spearman's rank correlation coefficient. Continuous variables were expressed as means or medians, and categorical variables were expressed as absolute and relative frequencies. Optimal cutoff thresholds were determined by receiver operating characteristic curve analysis. A p value <0.05 was considered to be statistically significant.

Results

Patient Background Characteristics

Table 1 shows the baseline clinical characteristics of the 64 study patients (48 men, 16 women) at the initiation of Atezo + Bev treatment. The median patient age was 70 (47–90) years. Thirty-seven (57.8%), 20 (31.3%), and 7 (10.9%) patients had Child-Pugh scores 5, 6, or 7, respectively. There were 41 patients (64.1%) who were being treated for hypertension. The median baseline UPCR of the study patients was 0.16 g/g Cr; 13 (20.3%) patients were positive for proteinuria (1 + on the dipstick test). Atezo + Bev was administered to 35 patients as first-line therapy and to 29 patients as second-line or subsequent therapy. The median number of treatment cycles was 6, and the median observation period was 8.1 months.

Treatment Outcome

Based on the RECIST 1.1 guidelines, the proportions of patients at the time of their best response were as follows: complete response 1.6%, partial response 23.4%, stable disease 53.1%, and progressive disease 21.9%. The objective response rate was 25.0%. The median survival time was not reached, and the median progression-free survival was 7.8 months.

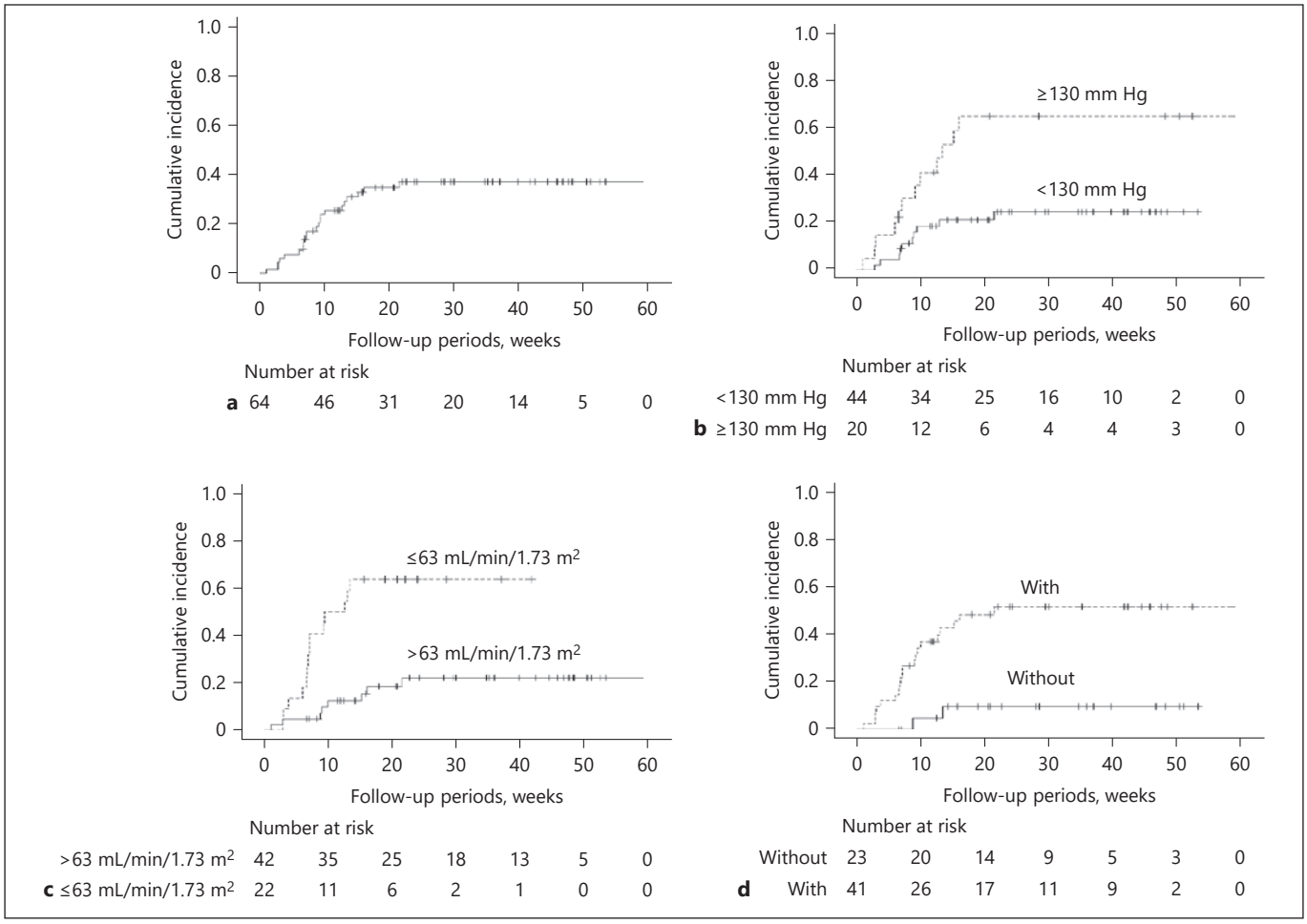

Fig. 1. Cumulative incidence of proteinuria. **a** All patients. **b** Systolic blood pressure. **c** Estimated glomerular filtration rate. **d** Treatment for hypertension.

Cumulative Incidence of Proteinuria

Figure 1a shows the cumulative incidence of proteinuria among all patients analyzed. The cumulative incidences of proteinuria at 6, 12, and 24 weeks were 9.4%, 25.0%, and 34.4%, respectively. Univariate analysis showed a relationship between proteinuria and the following variables: estimated glomerular filtration rate (eGFR), treatment for hypertension, SBP, and UPCR at baseline. Multivariate analysis showed that an eGFR ≤63 mL/min/1.73 m^2 (hazard ratio [HR], 3.807; 95% confidence interval [CI], 1.579–9.180; $p = 0.003$), treatment for hypertension (HR, 6.224; 95% CI, 1.614–24.010; $p = 0.008$), and SBP ≥130 mm Hg (HR, 2.649; 95% CI, 1.133–6.194; $p = 0.025$) were significant and independent risk factors of proteinuria (Table 2, Fig. 1b–d). The patients were divided into 4 groups based on whether or not at baseline they were taking aHT drugs and had an SBP ≥130 mm Hg at baseline: patients with SBP ≥130 mm Hg and taking aHT drugs had the highest risk of proteinuria, and patients with SBP <130 mm Hg and not taking aHT drugs had the lowest risk of proteinuria (Fig. 2).

Changes in ALBI Scores, Serum Alb Levels, and Serum Total Bil Levels

Figure 3 shows relative changes in ALBI scores, serum albumin levels, and serum total bilirubin levels in 50 patients who underwent 5 treatment cycles. There were 22 patients with and 28 patients without proteinuria. In the patients with proteinuria, ALBI scores worsened significantly at cycle 2 (−2.459 ± 0.425 vs. −2.286 ± 0.438, $p = 0.009$), cycle 4 (−2.299 ± 0.499, $p = 0.009$), and cycle 5 (−2.271 ± 0.491, $p = 0.017$), compared to those at baseline. Similarly, the serum albumin levels in patients with

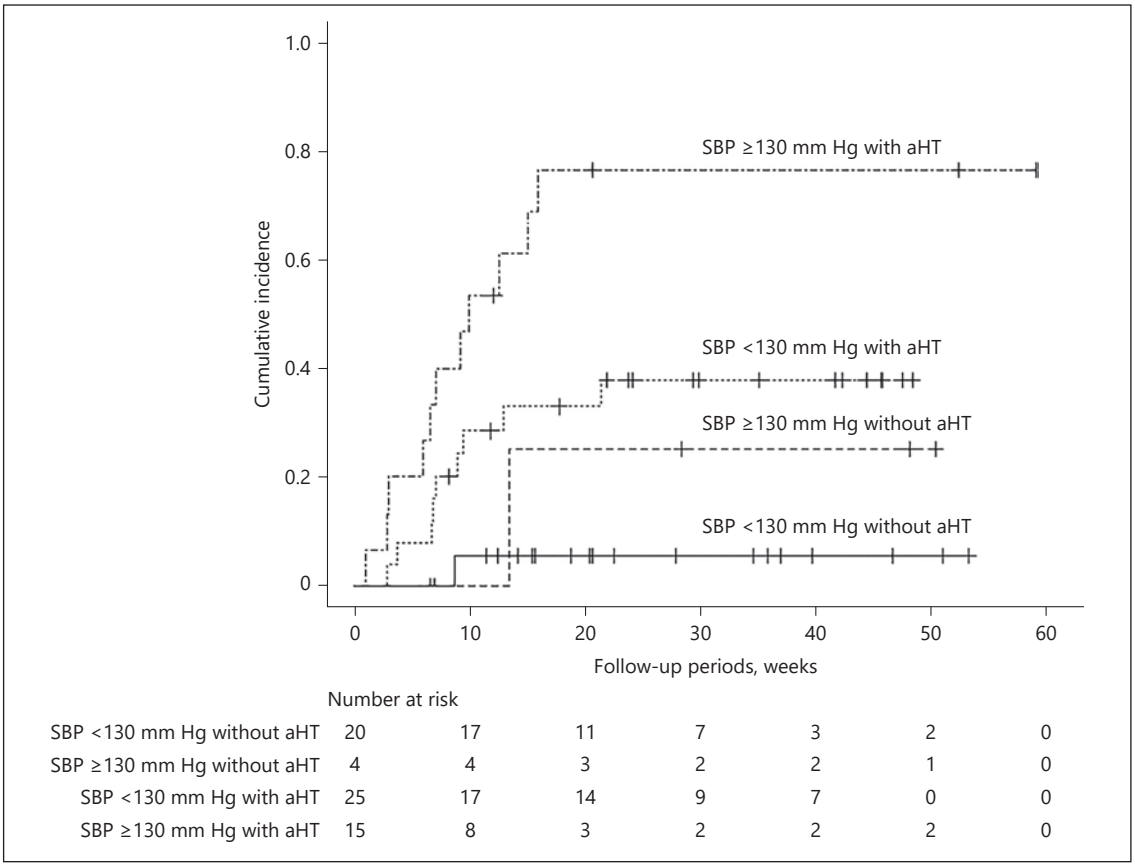

Fig. 2. Cumulative incidence of proteinuria, with patients divided into 4 groups according to systolic blood pressure and treatment with antihypertensive (aHT) agents.

Table 2. Univariate and multivariate analyses of risk factors for proteinuria during treatment

Variable	Univariate *p* value[a]	HR	Multivariate 95% CI	*p* value[b]
Sex (male vs. female)	0.336			
Etiology (viral vs. nonviral)	0.615			
ECOG PS (1 vs. 0)	0.779			
Child-Pugh score (6 or 7 vs. 5)	0.071			
mALBI grade (2b vs. 1 or 2a)	0.664			
eGFR (≤63 vs. >63) (mL/min/1.73 m^2)	<0.001	3.807	1.579–9.180	0.003
Treatment for hypertension (with vs. without)	0.002	6.224	1.614–24.010	0.008
Treatment of diabetes (with vs. without)	0.781			
SBP at baseline (≥130 vs. <130) (mm Hg)	0.002	2.649	1.133–6.194	0.025
DBP at baseline (≥69 vs. <69) (mm Hg)	0.091			
Macrovascular invasion (with vs. without)	0.468			
Extrahepatic metastasis (with vs. without)	0.856			
History of MTAs (with vs. without)	0.718			
UPCR at baseline (≥0.35 vs. <0.35) (g/g Cre)	<0.001			

HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; eGFR, estimated glomerular filtration rate; BP, blood pressure; MTA, molecular targeted agent; UPCR, urinary protein-to-creatinine ratio. [a] Log-rank test. [b] Cox proportional hazard regression.

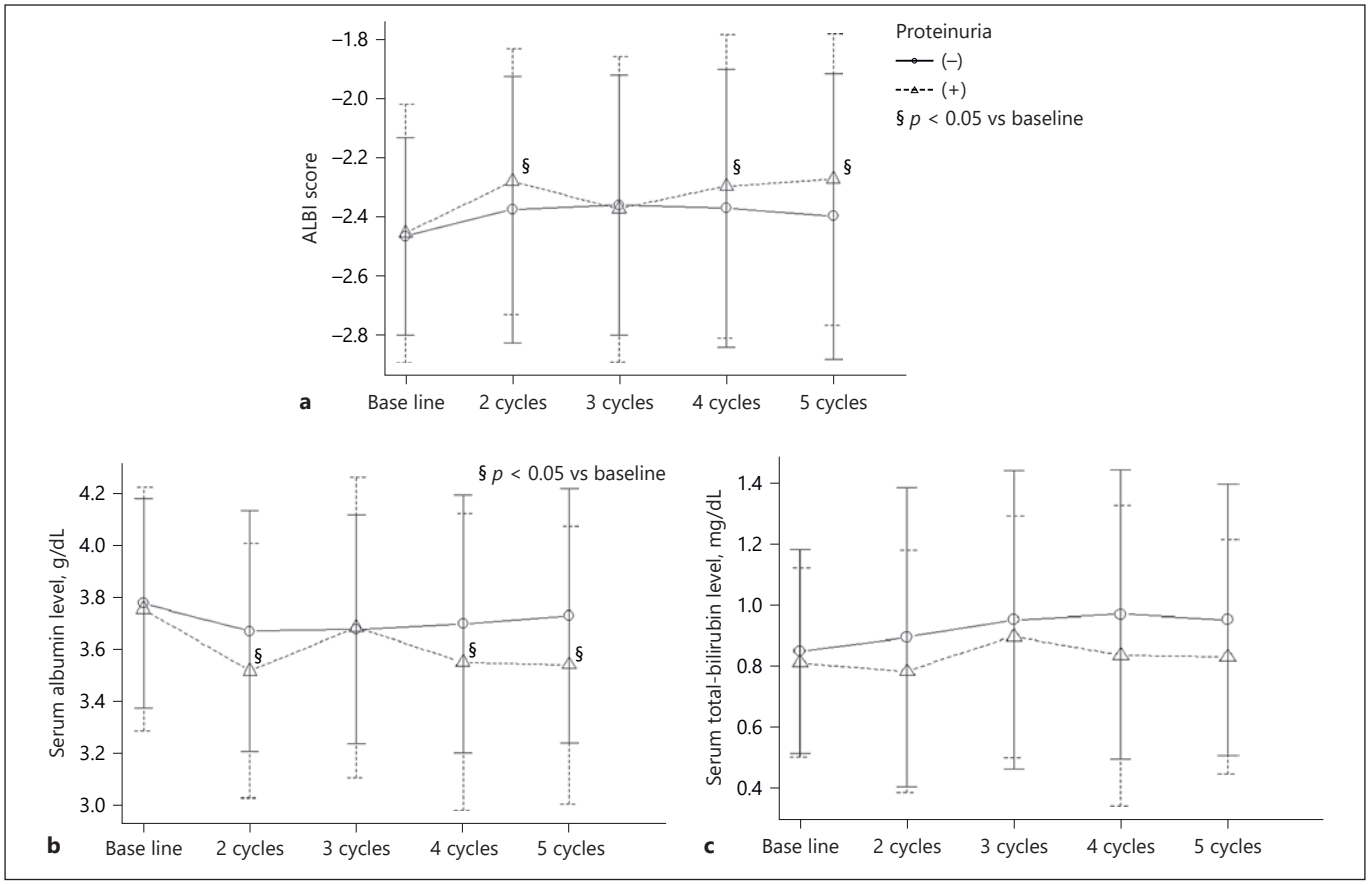

Fig. 3. Changes in albumin-bilirubin (ALBI) scores, serum albumin levels, and serum total bilirubin levels. Test: the paired *T* test. **a** ALBI scores. **b** Serum albumin levels. **c** Serum total bilirubin levels.

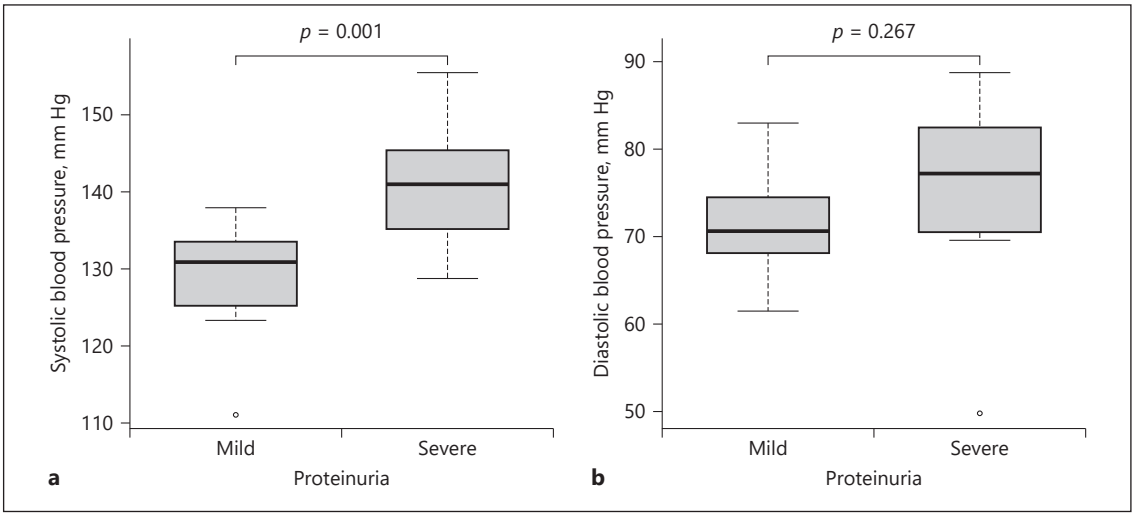

Fig. 4. Comparison of blood pressures during treatment between patients with severe proteinuria and patients with mild proteinuria. Severe proteinuria: a UPCR >2 g/g Cr. Test: the Mann-Whitney test. **a** Systolic blood pressure. **b** Diastolic blood pressure.

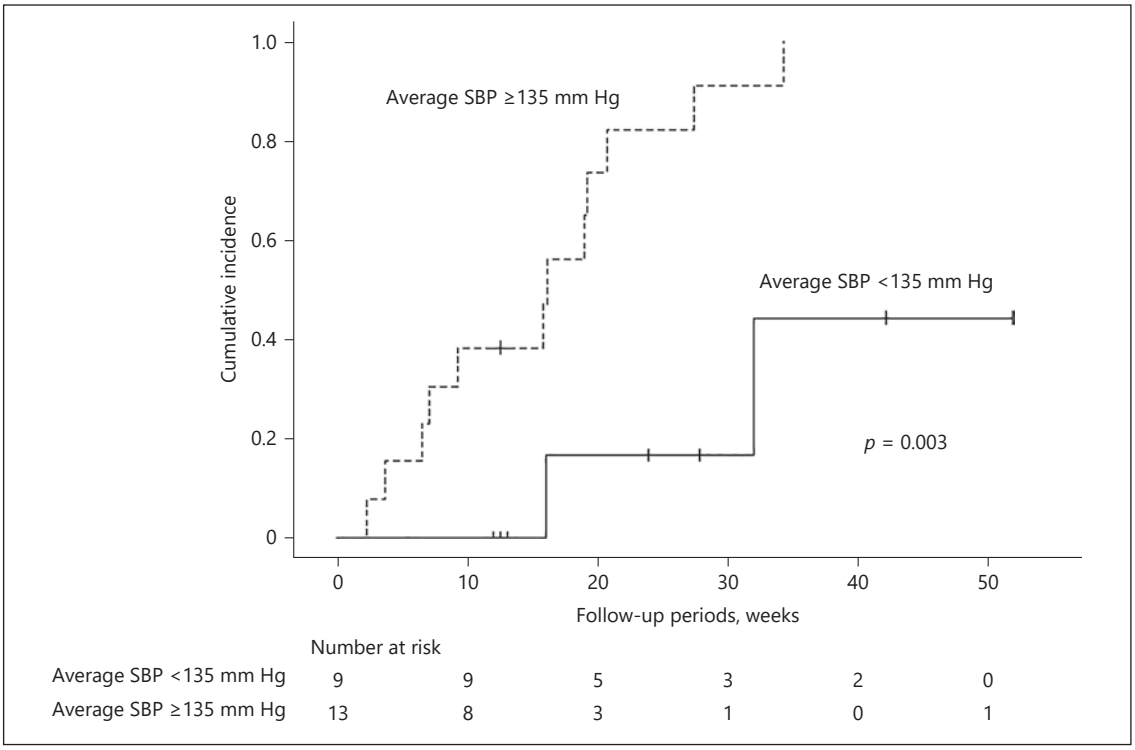

Fig. 5. Cumulative incidence of severe proteinuria according to mean systolic blood pressure (SBP). Severe proteinuria: a UPCR >2 g/g Cr.

Table 3. Univariate and multivariate analyses of risk factors for severe proteinuria during treatment

Variable	Univariate *p* value[a]	HR	Multivariate 95% CI	*p* value[b]
Sex (male vs. female)	0.180			
Etiology (viral vs. nonviral)	0.282			
ECOG PS (1 vs. 0)	0.607			
Child-Pugh score (6 or 7 vs. 5)	0.460			
mALBI grade (2b vs. 1 or 2a)	0.474			
eGFR (≤63 vs. >63) (mL/min/1.73 m^2)	0.114			
Treatment for hypertension (with vs. without)	0.759			
Treatment of diabetes (with vs. without)	0.601			
SBP at baseline (≥130 vs. <130) (mm Hg)	0.618			
DBP at baseline (≥69 vs. <69) (mm Hg)	0.761			
Macrovascular invasion (with vs. without)	0.725			
Extrahepatic metastasis (with vs. without)	0.151			
History of MTAs (with vs. without)	0.685			
UPCR at baseline (≥0.35 vs. <0.35) (g/g Cre)	0.022	3.326	0.882–12.540	0.076
Average SBP (≥135 vs. <135) (mm Hg)	0.003	6.909	1.436–33.230	0.016

HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; eGFR, estimated glomerular filtration rate; BP, blood pressure; MTA, molecular targeted agent; UPCR, urinary protein-to-creatinine ratio. [a] Log-rank test. [b] Cox proportional hazard regression.

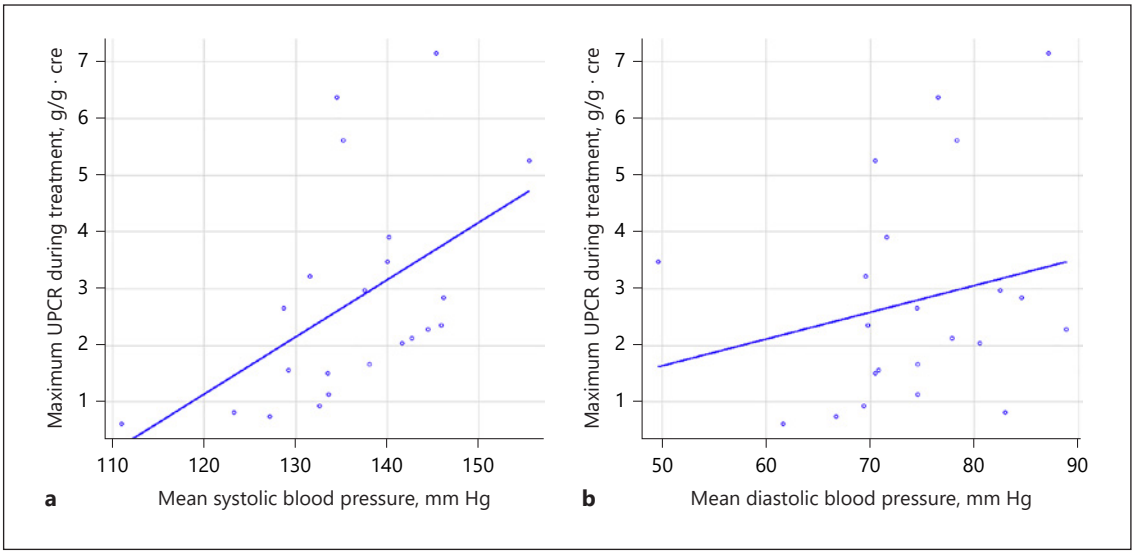

Fig. 6. Association of mean systolic and mean diastolic blood pressure with maximum UPCR recorded during treatment. **a** Mean systolic blood pressure: $r = 0.578$, $p = 0.005$. **b** Mean diastolic blood pressure: $r = 0.28$, $p = 0.207$.

proteinuria also had significantly deteriorated from baseline to cycle 2 (3.759 ± 0.457 vs. 3.527 ± 0.478, respectively; $p = 0.004$), to cycle 4 (3.554 ± 0.555, respectively; $p = 0.008$), and to cycle 5 (3.543 ± 0.532, respectively; $p = 0.021$). On the other hand, patients without proteinuria did not show these changes over the 5 cycles. The changes in serum total bilirubin levels of patients with or without proteinuria were not significant.

Cumulative Incidence of Severe Proteinuria among Patients with Proteinuria

Among 22 patients with proteinuria during treatment, 14 developed severe proteinuria (UPCR >2 g/g Cr). The patients with severe proteinuria had a significantly higher mean SBP during treatment compared to the patients with mild proteinuria (UPCR ≤2 g/g Cr) (Fig. 4). Univariate analysis showed a relationship between severe proteinuria and UPCR at baseline and a mean SBP during treatment. Multivariate analysis showed that a mean SBP during treatment ≥135 mm Hg was the only significant and independent risk factor of severe proteinuria (HR, 6.909; 95% CI, 1.436–33.230; $p = 0.016$) (Table 3, Fig. 5).

Figure 6 shows the correlation between mean SBP and DBP during treatment and maximum UPCR recorded during treatment in 22 patients with proteinuria. Significant positive correlations of mean SBP and maximum UPCR were detected ($r = 0.578$, $p = 0.005$).

Discussion

The aim of our study was to predict the early onset of proteinuria in patients with unresectable HCC treated with Atezo + Bev using factors before treatment. The cumulative incidence of proteinuria at 6, 12, and 24 weeks was 9.4%, 25.0%, and 34.4%, respectively. Our study found significant relationships between proteinuria and the following variables: SBP, treatment for hypertension, and eGFR at baseline. We also found that serum albumin levels and ALBI scores in patients with proteinuria were deteriorated. On the other hand, pretreatment factors could not predict the development of severe proteinuria, and the mean SBP during treatment was the only risk factor for development of severe proteinuria requiring interruption Bev. To our best knowledge, this is the first report to examine the risk factors for early onset of proteinuria in HCC patients treated with Atezo + Bev.

Since its approval in 2020, Atezo + Bev has been widely used for patients with unresectable HCC in clinical practice, and there are many published reports on the efficacy and safety of this combination [11, 12]. A phase 1 b study showed that the addition of Bev strengthened the antitumor effect of Atezo. Patients treated with Atezo + Bev had a longer progression-free survival than those treated with Atezo monotherapy [21]. In a real-world practice, Hatanaka et al. [12] reported on the negative

consequences regarding antitumor efficacy when Bev treatment was interrupted early during the treatment of patients with HCC. They showed that the early interruption of Bev treatment was a significant adverse factor associated with PFS ($p = 0.021$) and OS ($p = 0.008$), and that proteinuria was more frequently found in patients whose Bev treatment was interrupted than in those whose treatment was not interrupted (35.9% vs. 18.0%, $p = 0.005$). In other words, to maximize the antitumor effects of Atezo + Bev in patients with unresectable HCC, it is essential to prevent the interruption of Bev treatment by providing the timely and careful management of AEs such as proteinuria.

In our study, of the 22 patients with proteinuria, 14 (63.6%) showed severe proteinuria (UPCR >2 g/g Cr) requiring the interruption of Bev. These patients had higher mean SBP during treatment than patients without severe proteinuria. Based on previous research, hypertension and proteinuria may be related [22]. It is hypothesized that proteinuria may also result from increased intraglomerular pressure secondary to arterial hypertension. We also showed a positive correlation between mean SBP and maximum UPCR recorded during treatment. Therefore, the adequate control of BP during treatment may prevent the interruption of Bev treatment due to proteinuria.

Inhibitors of VEGF or the signaling of VEGF receptors (VEGFRs) induce hypertension resulting from the increased production of nitric oxide and the rarefaction of microvascular endothelial cells [23]. Proteinuria due to anti-VEGF/VEGFR agents is caused not only by disorders associated with elevated systemic and glomerular blood pressure (BP), but also by disruption of podocyte integrity [24–26]. In addition, thrombotic microangiopathy with reduced VEGF within the kidney was reported to result in profound glomerular injury [27].

Predictive factors for proteinuria in treatments using Bev for various cancers have already been reported [28–30]. Previous articles reported that drug dose, elevated BP, and certain types of aHT agents were risk factors for proteinuria. However, proteinuria that occurs during anti-VEGF treatment for patients with HCC has not yet been fully investigated. To date, the following 6 systemic therapies have been approved for the treatment of patients with unresectable HCC: Atezo + Bev, sorafenib, and lenvatinib as first-line treatments; and regorafenib, cabozantinib, and ramucirumab as second-line treatments [31–35]. All of these drugs have anti-VEGF/anti-VEGFR activity and therefore can cause hypertension and proteinuria.

In our study, patients with proteinuria had significantly worse serum albumin levels and ALBI scores. Although previous reports showed early deterioration of ALBI grade during Atezo + Bev treatment, the exact reason is unknown. However, in many reports, there was a temporary decline in liver function at cycle 2, and improvement was observed at cycle 3 and 4 [11, 36]. In this study, the ALBI grade and serum albumin levels in patients without onset of proteinuria worsened at cycle 2 but remained stable thereafter, consistent with previous reports. On the other hand, in patients with proteinuria, the ALBI grade, which had temporarily improved, worsened again in the 4th cycle. This change is newly observed, and the effect of proteinuria must be considered. However, if a decrease in ALBI grade was observed in patients with proteinuria due to the loss of albumin from the urine, this fact is unlikely to reflect a direct deterioration in hepatic reserve function.

Patients treated with Atezo + Bev for HCC are considered to have a higher risk for proteinuria than patients treated with other molecular targeted agents (MTAs) previously. First, the relative increase in patients with non-B, non-C hepatitis associated with HCC is a major problem. Nagaoki et al. [4] reported that patients with non-B, non-C hepatitis associated with HCC have a significantly higher rate of hypertension, type 2 diabetes, and dyslipidemia than patients with HCC associated with infections due to hepatis B and C. In our study, there were 28 (43.8%) patients with non-B, non-C hepatitis associated with HCC, which was a higher proportion than in the IMbrave150 trial (100/336, 29.8%). Second, Atezo + Bev is often used as second-line or subsequent therapy in clinical practice. Patients with a previous history of other MTAs may already have hypertension and proteinuria. This study included 29 (45.3%) patients with a previous history of MTA treatment. In fact, the incidence of proteinuria in our study was higher than in the IMbrave150 trial (34.4% vs. 20.1%) [8]. Our study might have consisted of many patients who already had risk factors for proteinuria. Third, the dose of Bev used to treat HCC is high, at 15 mg per kg of body weight. It has already been reported that there was a significant dose-dependent increase in the risk of proteinuria and hypertension in patients treated with Bev [28]. Thus, proteinuria must be very carefully managed in Atezo + Bev for patients with unresectable HCC.

This study has limitations. It was a retrospective study of a very small number of patients with a very short observation period. In addition, the associations between proteinuria and types of aHT agents and the changes in

antitumor effects caused by the withdrawal of Bev were not demonstrated. Actual measures for managing proteinuria are also issues in the future. Therefore, a more definitive conclusion requires a longer observation period and a larger number of study patients. Nevertheless, we have shown that SBP, treatment for hypertension, and eGFR were significant predictors of the early development of proteinuria in HCC patients treated with Atezo + Bev.

In conclusion, the BP control is an extremely important factor in the management of proteinuria in patients with HCC treated with Atezo + Bev. We believe that this information will be very useful for the management of patients receiving Atezo + Bev in real-world practice.

Statement of Ethics

This study was approved by the Ethics Review Committee of Hiroshima University (project identification code number E-2300) on December 15, 2020. This was a retrospective analysis of records stored in a database. Written informed consent was obtained from participants to participate in the study. It received official approval that was based on the Guidelines for Clinical Research issued by the Ministry of Health and Welfare in Japan. All procedures complied with the Declaration of Helsinki.

Conflict of Interest Statement

Michio Imamura has received honoraria and research funding from Bristol Myers Squibb.

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Author Contributions

Yuwa Ando: conceptualization, formal analysis, and original draft; Tomokazu Kawaoka: conceptualization, review, and editing; Masanari Kosaka, Yuki Shirane, Yusuke Johira, Ryoichi Miura, Serami Murakami, Shigeki Yano, Kei Amioka, Kensuke Naruto, and Yumi Kosaka: data curation; Shinsuke Uchikawa, Kenichiro Kodama, Hatsue Fujino, Takashi Nakahara, Atsushi Ono, Eisuke Murakami, Masami Yamauchi, Wataru Okamoto, Shoichi Takahashi, and Michio Imamura: treated the patients; Hiroshi Aikata: review and editing. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301–14.
2 Singal AG, El-Serag HB. Hepatocellular carcinoma from epidemiology to prevention: translating knowledge into practice. Clin Gastroenterol Hepatol. 2015;13(12):2140–51.
3 Tateishi R, Uchino K, Fujiwara N, Takehara T, Okanoue T, Seike M, et al. A nationwide survey on non-B, non-C hepatocellular carcinoma in Japan: 2011-2015 update. J Gastroenterol. 2019;54(4):367–76.
4 Nagaoki Y, Hyogo H, Ando Y, Kosaka Y, Uchikawa S, Nishida Y, et al. Increasing incidence of non-HBV- and non-HCV-related hepatocellular carcinoma: single-institution 20-year study. BMC Gastroenterol. 2021;21(1):306.
5 Herbst RS, Soria J-C, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014;515(7528):563–7.
6 Ferrara N, Hillan KJ, Novotny W. Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy. Biochem Biophys Res Commun. 2005;333(2):328–35.
7 Finn RS, Bentley G, Britten CD, Amado R, Busuttil RW. Targeting vascular endothelial growth factor with the monoclonal antibody bevacizumab inhibits human hepatocellular carcinoma cells growing in an orthotopic mouse model. Liver Int. 2009;29(2):284–90.
8 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20):1894–905.
9 European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu;European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.
10 Liu X, Lu Y, Qin S. Atezolizumab and bevacizumab for hepatocellular carcinoma: mechanism, pharmacokinetics and future treatment strategies. Future Oncol. 2021;17(17):2243–56.
11 Ando Y, Kawaoka T, Kosaka M, Shirane Y, Johira Y, Miura R, et al. Early tumor response and safety of atezolizumab plus bevacizumab for patients with unresectable hepatocellular carcinoma in real-world practice. Cancers. 2021 Aug 5;13(16):3958.
12 Hatanaka T, Hiraoka A, Tada T, Hirooka M, Kariyama K, Tani J, et al. Association of early bevacizumab interruption with efficacy of atezolizumab plus bevacizumab for advanced hepatocellular carcinoma: a landmark analysis. Hepatol Res. 2022 Jan 25;52(5):462–70.
13 Ginsberg JM, Chang BS, Matarese RA, Garella S. Use of single voided urine samples to estimate quantitative proteinuria. N Engl J Med. 1983;309(25):1543–6.
14 Yang CY, Chen FA, Chen CF, Liu WS, Shih CJ, Ou SM, et al. Diagnostic accuracy of urine protein/creatinine ratio is influenced by urine concentration. PLoS One. 2015;10(9):e0137460.
15 Wu S, Kim C, Baer L, Zhu X. Bevacizumab increases risk for severe proteinuria in cancer patients. J Am Soc Nephrol. 2010;21(8):1381–9.
16 Hirai T, Shuji Y, Takiyama M, Hanada K, Itoh T. Renin-angiotensin system inhibitors for countering proteinuria induced by angiogenesis inhibitors: a retrospective observational analysis. Cancer Chemother Pharmacol. 2019;84(1):195–202.
17 Schwartz LH, Seymour L, Litière S, Ford R, Gwyther S, Mandrekar S, et al. Recist 1.1-standardisation and disease-specific adaptations: perspectives from the recist working group. Eur J Cancer. 2016;62:138–45.

18 Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015;33(6):550–8.
19 Hiraoka A, Kumada T, Tsuji K, Takaguchi K, Itobayashi E, Kariyama K, et al. Validation of modified ALBI grade for more detailed assessment of hepatic function in hepatocellular carcinoma patients: a multicenter analysis. Liver Cancer. 2019;8(2):121–9.
20 Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transpl. 2013;48(3):452–8.
21 Lee MS, Ryoo BY, Hsu CH, Numata K, Stein S, Verret W, et al. Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study. Lancet Oncol. 2020;21(6):808–20.
22 Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol. 2005;23(4):792–9.
23 Sane DC, Anton L, Brosnihan KB. Angiogenic growth factors and hypertension. Angiogenesis. 2004;7(3):193–201.
24 Cosmai L, Gallieni M, Liguigli W, Porta C. Renal toxicity of anticancer agents targeting vascular endothelial growth factor (VEGF) and its receptors (VEGFRs). J Nephrol. 2017;30(2):171–80.
25 Ronco P. Proteinuria; is it all in the foot? J Clin Invest. 2007;117(8):2079–82.
26 Ahima RS. Linking adiponectin to proteinuria. J Clin Invest. 2008;118(5):1619–22.
27 Eremina V, Jefferson JA, Kowalewska J, Hochster H, Haas M, Weisstuch J, et al. VEGF inhibition and renal thrombotic microangiopathy. N Engl J Med. 2008;358(11):1129–36.
28 Zhu X, Wu S, Dahut WL, Parikh CR. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. Am J Kidney Dis. 2007;49(2):186–93.
29 Nihei S, Sato J, Harada T, Kuyama S, Suzuki T, Waga N, et al. Antiproteinuric effects of renin-angiotensin inhibitors in lung cancer patients receiving bevacizumab. Cancer Chemother Pharmacol. 2018;81(6):1051–9.
30 Kanbayashi Y, Ishikawa T, Tabuchi Y, Sakaguchi K, Ouchi Y, Otsuji E, et al. Predictive factors for the development of proteinuria in cancer patients treated with bevacizumab, ramucirumab, and aflibercept: a single-institution retrospective analysis. Sci Rep. 2020;10(1):2011.
31 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10(1):25–34.
32 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163–73.
33 Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56–66.
34 Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med. 2018;379(1):54–63.
35 Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(2):282–96.
36 Hiraoka A, Kumada T, Tada T, Hirooka M, Kariyama K, Tani J, et al. Atezolizumab plus bevacizumab treatment for unresectable hepatocellular carcinoma: early clinical experience. Cancer Rep. 2022;5(2):e1464.