Research Square

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Prognostic Value of the C-Reactive Protein-Albumin Ratio in Patients with Advanced Urothelial Carcinoma Treated with Enfortumab Vedotin Plus Pembrolizumab

Taisuke Jo
Kawasaki Medical School: Kawasaki Ika Daigaku
Taizo Uchimoto
Osaka Medical and Pharmaceutical University: Osaka Ika Yakka Daigaku
Kyosuke Nishio
Kawasaki Medical School: Kawasaki Ika Daigaku
Heima Niigawa
Kawasaki Medical School: Kawasaki Ika Daigaku
Hirofumi Morinaka
Kawasaki Medical School: Kawasaki Ika Daigaku
Shintaro Takahashi
Kawasaki Medical School: Kawasaki Ika Daigaku
Ryoichi Maenosono
Osaka Medical and Pharmaceutical University: Osaka Ika Yakka Daigaku
Yuki Yoshikawa
Osaka Medical and Pharmaceutical University: Osaka Ika Yakka Daigaku
Takuya Tsujino
Osaka Medical and Pharmaceutical University: Osaka Ika Yakka Daigaku
Wataru Fukuokaya
The Jikei University School of Medicine: Tokyo Jikeikai Ika Daigaku
Keiichiro Mori
The Jikei University School of Medicine: Tokyo Jikeikai Ika Daigaku
Takafumi Yanagisawa
The Jikei University School of Medicine: Tokyo Jikeikai Ika Daigaku
Lan Inoki
Kindai University Faculty of Medicine Hospital: Kinki Daigaku Igakubu Daigaku Byoin
Mamoru Hashimoto
Kindai University Faculty of Medicine Hospital: Kinki Daigaku Igakubu Daigaku Byoin
Takuhisa Nukaya
Fujita Health University: Fujita Ika Daigaku

Masanobu Saruta
Fujita Health University: Fujita Ika Daigaku
Keita Tamura
Hamamatsu University School of Medicine: Hamamatsu Ika Daigaku
Asuka Sano
Hamamatsu University School of Medicine: Hamamatsu Ika Daigaku
Takahiro Kimura
The Jikei University School of Medicine: Tokyo Jikeikai Ika Daigaku
Kazutoshi Fujita
Kindai University Faculty of Medicine Hospital: Kinki Daigaku Igakubu Daigaku Byoin
Kiyoshi Takahara
Fujita Health University: Fujita Ika Daigaku
Teruo Inamoto
Hamamatsu University School of Medicine: Hamamatsu Ika Daigaku
Haruhito Azuma
Osaka Medical and Pharmaceutical University: Osaka Ika Yakka Daigaku
Kazumasa Komura
k.komura@med.kawasaki-m.ac.jp

Kawasaki Medical School: Kawasaki Ika Daigaku https://orcid.org/0000-0003-4157-1929

Research Article

Keywords: Urothelial carcinoma, Enfortumab vedotin, Pembrolizumab, C-reactive protein-Albumin ratio

Posted Date: September 14th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10770109/v1

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Abstract

Background

While enfortumab vedotin plus pembrolizumab (EVP) is a standard first-line treatment for advanced urothelial carcinoma (aUC), reliable prognostic biomarkers remain lacking. This study evaluated the prognostic value of the pretreatment C-reactive protein-Albumin ratio (CAR) in aUC patients treated with EVP.

Methods

We retrospectively analyzed 212 patients with aUC treated with EVP in a multicenter cohort. The optimal CAR cutoff was determined by receiver operating characteristic (ROC) analysis using the Youden index. Survival outcomes were assessed using Kaplan–Meier and multivariable Cox regression analyses.

Results

Over a median follow-up of 6.9 months, ROC analysis showed that CAR had the highest predictive performance (concordance index, 0.724) among putative systemic inflammation markers, including NLR, PLR, and LDH. Using the optimal 4.0 cutoff, the high-CAR group (≥ 4.0, n = 78) exhibited significantly shorter median overall survival (OS) (10.2 months vs. not reached; P < 0.001) and progression-free survival (PFS) (7.4 vs. 11.5 months; P = 0.001) than the low-CAR group (< 4.0, n = 134). Multivariable analysis identified elevated CAR as an independent predictor of poor OS (hazard ratio, 3.47; 95% confidence interval, 1.57–7.66; P = 0.002). Although the objective response rate difference was not statistically significant (67.9% vs. 55.1%; P = 0.076), high CAR was associated with a significantly shorter duration of response among responders (10.6 months vs. not reached; P = 0.048).

Conclusion

Pretreatment CAR is a durable biomarker for predicting survival outcomes and response durability in aUC patients receiving EVP, which can assist in clinical risk stratification.

1. Introduction

Advanced urothelial carcinoma (aUC), defined as locally advanced or metastatic urothelial carcinoma, is a highly aggressive malignancy arising from the urothelium [1]. Until recently, treatment options were limited primarily to platinum-based chemotherapy [2, 3]. However, the therapeutic landscape of aUC has changed dramatically over the past decade with the introduction of several novel agents, including immune checkpoint inhibitors (CPIs) [4], fibroblast growth factor receptor (FGFR) inhibitors [5], and antibody–drug conjugates (ADCs) [6, 7]. Among these, the combination of enfortumab vedotin (EV), an

ADC targeting Nectin-4, and pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, was approved in 2024 based on the results of the EV-302 trial [8]. In this phase III study of patients with previously untreated locally advanced or metastatic urothelial carcinoma, EV plus pembrolizumab (EVP) significantly improved clinical outcomes compared with platinum-based chemotherapy, achieving a median overall survival (OS) of 31.5 months versus 16.1 months and a median progression-free survival (PFS) of 12.5 months versus 6.3 months [8]. Although EVP has rapidly become the standard first-line treatment for patients with aUC in real-world clinical practice, biomarkers capable of predicting survival outcomes and durability of response remain poorly established. Previous studies have demonstrated that blood-based biomarkers reflecting systemic inflammation and nutritional status, such as the C-reactive protein-Albumin ratio (CAR; CRP expressed in mg/L and serum albumin in g/dL), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lactate dehydrogenase (LDH) are associated with prognosis in various malignancies [9, 10, 11, 12, 13, 14, 15].

In the present study, we investigated the clinical utility of systemic inflammation and nutritional status–related biomarkers in patients with advanced urothelial carcinoma treated with EVP, with particular emphasis on the prognostic value of CAR for survival outcomes.

2 Patients and Methods

2.1 Study Cohort

The present study was conducted using a multi-institutional dataset including Osaka Medical and Pharmaceutical University (Osaka, Japan), the Jikei University School of Medicine (Tokyo, Japan), Kindai University Hospital (Osaka, Japan), Fujita Health University School of Medicine (Aichi, Japan), Hamamatsu University School of Medicine, (Shizuoka, Japan) and Kawasaki Medical School (Okayama, Japan) between October 2024 and February 2026. The study protocol was approved by the institutional review board of the principal institution, Osaka Medical and Pharmaceutical University (approval number: RIN-750-2571), and was conducted in accordance with the principles of the Declaration of Helsinki [16]. We included patients who were pathologically diagnosed with urothelial carcinoma and received treatment with EVP. Treatment response to EVP was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [17]. A total of 246 patients with aUC were included in the present study.

2.2 Follow-up

EVP was administered according to the approved regimen. EV was intravenously infused at a dose of 1.25 mg/kg over 30 minutes on days 1 and 8 of each 21-day cycle, while pembrolizumab was administered intravenously at a fixed dose of 200 mg on day 1 of each cycle [8]. During the follow-up period, radiographic assessments were performed using computed tomography (CT) scans of the chest, abdomen, and pelvis. Dose reduction, treatment discontinuation, or extension of the dosing interval of EVP was determined at the discretion of the treating physician and according to the patient's preference.

2.3 Clinical Variables

The primary objective of this study was to evaluate the prognostic value of the CAR in patients with aUC treated with EVP, particularly with respect to OS and PFS. Secondary objectives included assessment of the association between CAR and treatment response, including the objective response rate (ORR) and duration of response (DOR). Receiver operating characteristic (ROC) curve analyses were performed to determine the optimal cutoff values of several blood-based biomarkers, including the CAR, NLR, PLR and LDH. The optimal cutoff value for each biomarker was determined using the Youden index, which maximizes the difference between the true-positive rate and false-positive rate. OS and PFS were estimated using the Kaplan–Meier method. OS was defined as the time from initiation of EVP treatment to death from any cause or last follow-up. PFS was defined as the time from initiation of EVP treatment to clinical or radiographic disease progression or last follow-up.

Clinical variables assessed at the initiation of EVP treatment included age (< 75 years vs. ≥ 75 years), sex (male vs. female), primary tumor site (bladder vs. upper urinary tract), histology, eastern cooperative oncology group performance status (ECOG-PS) (0 vs. ≥ 1), and serum biomarkers including CAR, NLR, PLR and LDH.

2.4 Statistical Analysis

For our statistical analyses, we evaluated the distribution of each factor using contingency tables and applied Chi-square or Fisher's exact tests for categorical variables. The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. Based on these results, we employed either the Student's t-test or a one-way analysis of variance for variables with a normal distribution. For non-normally distributed variables, Wilcoxon or Kruskal–Wallis tests were utilized. Survival outcomes were estimated using Kaplan–Meier curves, with differences between groups analyzed via the log-rank test. All statistical tests were two-sided, and P-values less than 0.05 were deemed statistically significant. Univariate and multivariable Cox proportional hazards regression analyses were performed to identify prognostic factors associated with OS and PFS. The data analysis was conducted using JMP® 19 software (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism (GraphPad Software, La Jolla, CA, USA).

3 Results

3.1 Characteristics of the Cohort

Figure 1 shows the patient selection flowchart. A total of 246 patients with aUC who received EVP were initially identified. Among these, 31 patients without radiographic response assessment and 3 patients without available blood examination data were excluded, leaving 212 patients for the final analysis (Fig. 1). The baseline clinical characteristics of the 212 patients at the initiation of EVP therapy are summarized in Table 1. The median age was 75 years. The median follow-up period was 6.9 months for the entire cohort and 7.4 months for patients who were alive at the last follow-up. A total of 160 patients (75.5%) had pathologically confirmed pure urothelial carcinoma (**Table 1**). During the follow-up period, 43

patients (20.2%) died. The median OS was not reached, whereas the median PFS was 11.1 months. The best overall response to EVP therapy was complete response (CR) in 27 patients (13%), partial response (PR) in 107 patients (50%), stable disease (SD) in 56 patients (26%), and progressive disease (PD) in 22 patients (10%). The ORR and disease control rate (DCR) were 63% and 89%, respectively.

3.2 CAR as a Reliable Indicator Derived from Peripheral Blood Tests

We first performed ROC curve analysis to determine the optimal cutoff values for several clinical indicators obtained from blood examinations to predict OS in patients treated with EVP (Fig. 2). Among the evaluated biomarkers, the CAR showed the highest predictive performance, with a concordance index (C-index) of 0.724 (95% confidence interval [CI], 0.629–0.802), which was significantly higher than those of the other indicators, including NLR (C-index: 0.611, P = 0.004), PLR (C-index: 0.579, P = 0.006), and serum LDH (C-index: 0.587, P = 0.051) (Fig. 2). The optimal cutoff value for CAR, determined by the Youden index for predicting the OS to EVP, was 4.0. Using this cutoff value, 134 patients (63%) were classified into the low-CAR group (CAR < 4.0) and 78 patients (37%) into the high-CAR group (CAR ≥ 4.0).

Kaplan–Meier analysis demonstrated that patients with CAR ≥ 4.0 had significantly shorter OS than those with CAR < 4.0: the median OS was not reached in the low-CAR group and was 10.2 months in the high-CAR group (P < 0.001) (Fig. 3a). Similarly, PFS was significantly shorter in patients with CAR ≥ 4.0 than in those with CAR < 4.0 (P = 0.001). The median PFS was 11.5 months in the low-CAR group and 7.4 months in the high-CAR group (Fig. 3b). The ORR was 67.9% in the low-CAR group and 55.1% in the high-CAR group, whereas the difference was not statistically significant (P = 0.076) (Fig. 4a). Among patients who achieved an objective response, the median DOR was significantly shorter in the high-CAR group than in the low-CAR group (P = 0.048) (Fig. 4b). The median DOR was not reached in patients with CAR < 4.0, whereas it was 10.6 months in patients with CAR ≥ 4.0.

3.3 Prognostic Value of the CAR for Treatment Outcomes in EVP

To identify prognostic factors for OS, univariate and multivariate Cox proportional hazards regression analyses were performed (**Table 2**). The optimal cutoff values for each blood-based biomarker were determined using the Youden index based on ROC curve analysis (Fig. 2). In the univariate analysis, ECOG-PS ≥ 1 (hazard ratio [HR], 3.14; 95% confidence interval [CI], 1.72–5.73; P = 0.001), CAR ≥ 4.0 (HR, 4.98; 95% CI, 2.62–9.48; P < 0.001), NLR ≥ 5.6 (HR, 3.28; 95% CI, 1.79–6.00; P = 0.001), PLR ≥ 240 (HR, 2.05; 95% CI, 1.12–3.73; P = 0.019), and LDH ≥ 213 U/L (HR, 2.50; 95% CI, 1.37–4.55; P = 0.003) were significantly associated with worse OS.

In the multivariable analysis, ECOG-PS ≥ 1 (HR, 2.08; 95% CI, 1.01–4.29; P = 0.046) and CAR ≥ 4.0 (HR, 3.47; 95% CI, 1.57–7.66; P = 0.002) remained independent prognostic factors for OS. These findings

indicate that an elevated CAR at the initiation of EVP therapy is an independent predictor of poor survival outcomes in patients with aUC.

4 Discussion

ADCs have emerged as an important therapeutic modality for advanced urothelial carcinoma [18]. Recently, EVP therapy has demonstrated remarkable efficacy and has become standard first-line treatment for patients with aUC [8]. However, biomarkers that can predict survival outcomes and durability of response in patients receiving EVP remain poorly established. In the present study, we evaluated the clinical significance of the CAR in patients treated with EVP. Our study showed that patients with high-CAR had significantly shorter OS and PFS than those with low-CAR. Although the difference did not reach statistical significance, the ORR tended to be lower in the high-CAR group. However, among patients who achieved an objective response, the DOR was significantly shorter in the high-CAR group, suggesting that systemic inflammation and poor nutritional status may affect the durability of treatment efficacy rather than the initial tumor response.

Previous studies have reported that inflammation-based biomarkers, including the CAR, are associated with poor prognosis in patients with urothelial carcinoma receiving chemotherapy or immune checkpoint inhibitors [12, 13]. Consistent with these findings, our ROC analysis found that CAR showed superior predictive performance compared with NLR, PLR and serum LDH, indicating that CAR may represent a practical and readily available biomarker for risk stratification before EVP initiation. The biological mechanisms underlying the association between elevated CAR and poor clinical outcomes remain speculative. Elevated C-reactive protein reflects systemic inflammation mediated by pro-inflammatory cytokines, whereas hypoalbuminemia is associated with malnutrition and impaired host immunity [19, 20, 21]. Therefore, a high CAR may indicate both an unfavorable inflammatory state and reduced physiological reserve, potentially leading to inferior treatment efficacy and survival outcomes [20]. Interestingly, although ORR was not significantly different between the two groups, patients with elevated CAR experienced a significantly shorter DOR. These findings suggest that CAR may be more strongly associated with the maintenance of antitumor response than with initial tumor shrinkage. Further biological investigations are warranted to clarify the mechanisms responsible for this observation.

Several limitations should be acknowledged. First, this study was retrospective and conducted across multiple institutions with a relatively limited sample size, which may have introduced selection bias. Second, the median follow-up period was short because EVP has only recently been introduced into clinical practice. Third, molecular biomarkers that may influence treatment efficacy, such as Nectin-4 [22] expression, PD-L1 status [23], and genomic alterations including FGFR3 [24], were not evaluated. Finally, the optimal cutoff value for CAR requires external validation in independent cohorts.

In conclusion, our findings suggest that pretreatment CAR is a simple, inexpensive, and widely available biomarker associated with treatment durability and survival outcomes in patients receiving EVP therapy.

Prospective multicenter studies with larger cohorts are warranted to validate these findings and to establish the clinical utility of CAR for patient stratification and treatment decision-making.

Declarations

Competing Interests

Takahiro Kimura is a paid consultant/advisor of Astellas, Bayer, Janssen, Sanofi and Takeda.

Ethics Approval

This study was approved by the Institutional Review Board (IRB) from Osaka Medical and Pharmaceutical University (approval number: RIN-750-2571, approved on 4th February 2025). This observational study adhered to ethical principles aligned with the Declaration of Helsinki, the International Conference on Harmonisation's Good Clinical Practice guidelines, Good Pharmacoepidemiology Practices, and relevant laws for noninterventional and observational studies.

Consent to Participate

The requirement for written informed consent was waived because of the retrospective nature of the study, and patients were given the opportunity to opt out.

Consent to Publish

Not applicable.

Funding

Kazumasa Komura was partially supported by Grant-in-Aid No. 25K02776 (Japan Society for the Promotion of Science: JSPS).

Author Contributions

TJo: conceptualization, data curation, analysis, investigation, methodology, software, visualization, writing original draft, supervision. TUchimoto: data curation, analysis, investigation, methodology, software, visualization. KNishio: data curation, analysis. HNiigawa: data curation. HMorinaka: data curation. STakahashi: data curation. RMaenosono: investigation, data curation, validation. YYoshikawa: data curation, analysis. TTsujino: data curation, analysis. WFukuokaya: investigation, data curation, validation. KMori: data curation, analysis. TYanagisawa: data curation, analysis. LInoki: investigation,

data curation, validation. MHashimoto: data curation, analysis. TNukaya: investigation, data curation, validation. MSaruta: data curation, analysis. KTamura: investigation, data curation, validation. ASano: data curation, analysis. TKimura: supervision. KFujita: supervision. KTakahara: supervision. TInamoto: supervision. HAzuma: supervision. KKomura: data curation, investigation, writing the original draft, and supervision.

Acknowledgments

The authors thank all patients and investigators involved in this study.

Data Availability

The data from this study can be accessed by academic and commercial partners upon a reasonable request, subject to Institutional Review Board (IRB) approval and a data use agreement. For further details or to reanalyze the study's data, contact the Lead Contact at k.komura@med.kawasaki-m.ac.jp.

Code Availability

Not applicable.

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Tables

Tables 1 and 2 are available in the Supplementary Files section.

Figures

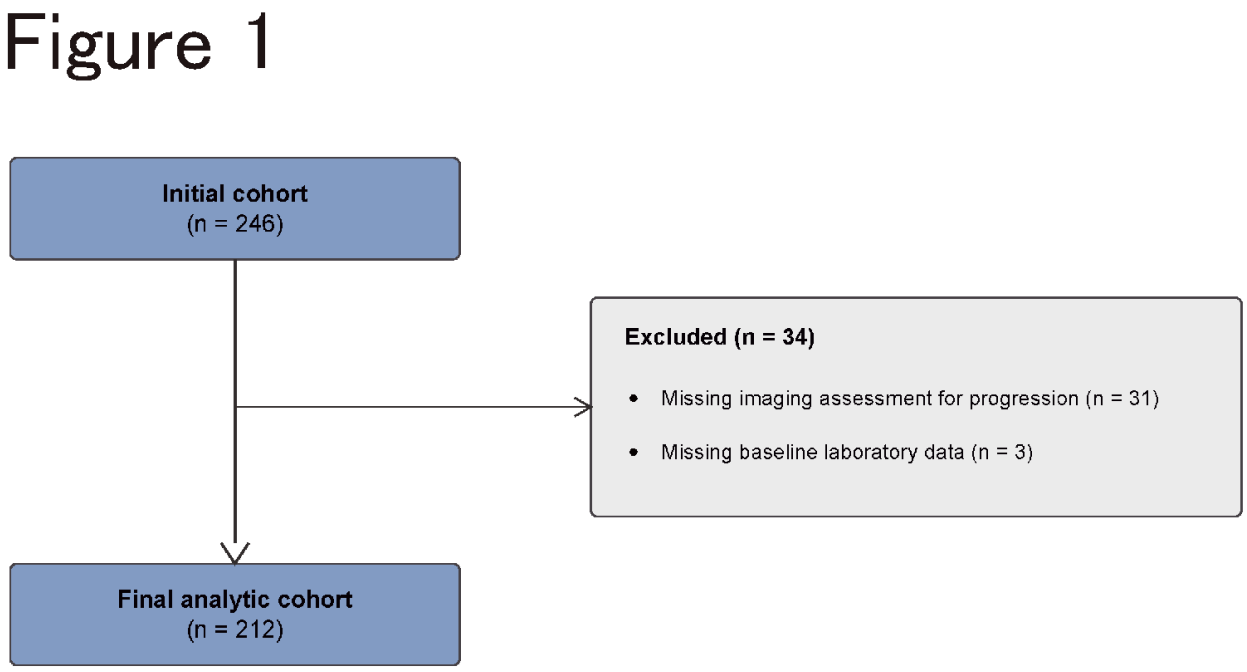
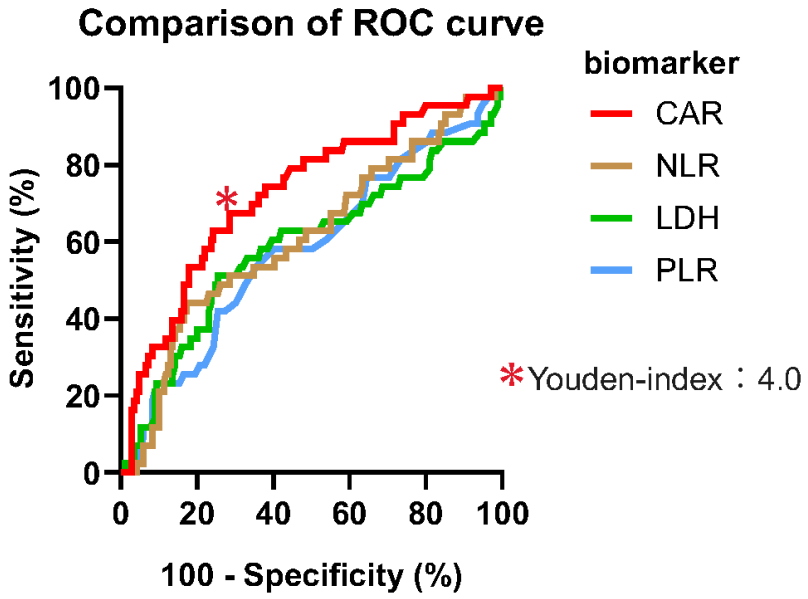


Figure 1

Flowchart of patient selection. A total of 246 patients who received enfortumab vedotin plus pembrolizumab (EVP) therapy were initially identified. 34 patients were excluded because of missing imaging assessment for progression (n = 31) or missing baseline laboratory data (n = 3), leaving 212 patients for the final analysis.

Figure 2



Comparison of C-index among putative serum biomarkers for predicting the lethality in 212 aUC patients treated with EVP.

biomarker	c-index	(95 % CI)	Youden-index	Sensitivity	Specificity	P-value
CAR	0.724	(0.629-0.802)	4.0	0.674	0.716	ref
NLR	0.611	(0.509-0.703)	5.6	0.442	0.828	0.004*
PLR	0.579	(0.478-0.674)	240	0.535	0.645	0.006*
LDH	0.587	(0.479-0.688)	213	0.512	0.746	0.051

aUC: advanced urothelial carcinoma, EVP: enfortumab vedotin and pembrolizumab, CI: confidence interval, CAR: c-reactive protein/albumin ratio, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LDH: lactate dehydrogenase, ref: reference, *denotes P-value < 0.05.

Figure 2

The receiver operating characteristic (ROC) curves for pretreatment biomarkers, including the C-reactive protein-Albumin ratio (CAR), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and serum lactate dehydrogenase (LDH), for predicting lethality (as a binary outcome) in patients treated with enfortumab vedotin plus pembrolizumab (EVP) are presented, along with the concordance index (C-index) and Youden index for each indicator. *CI*, confidence interval; *Ref*, reference

Figure 3

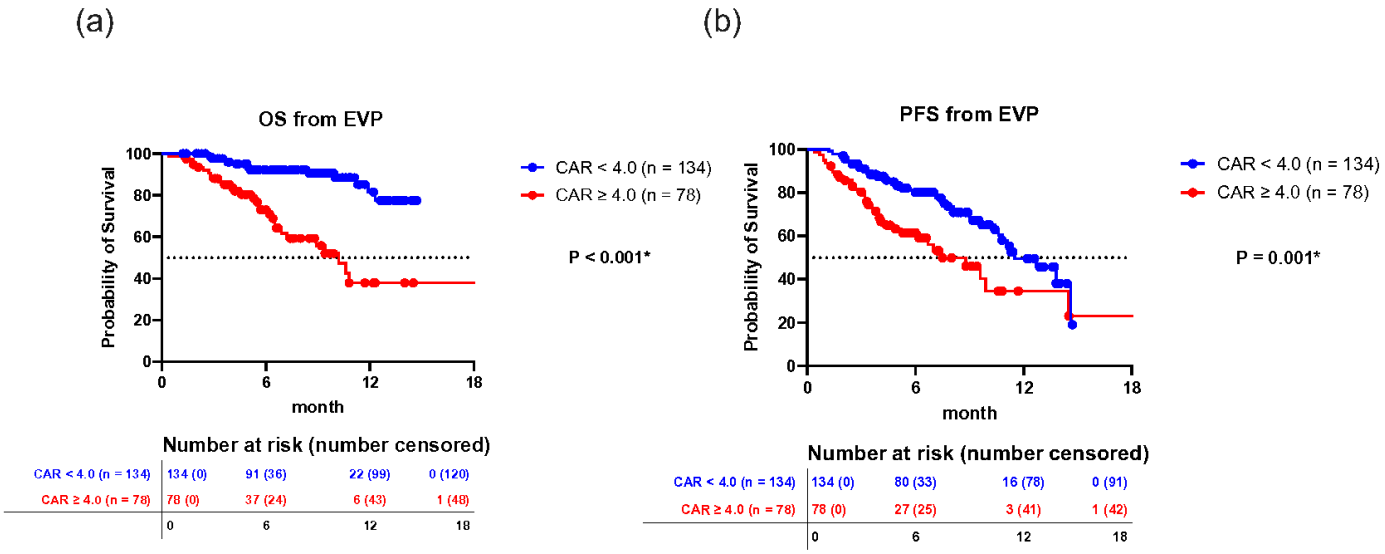


Figure 3

(a) Kaplan–Meier curves of overall survival (OS) from the initiation of enfortumab vedotin plus pembrolizumab (EVP) stratified by pretreatment C-reactive protein-Albumin ratio (CAR) (< 4.0 vs. ≥ 4.0).

(b) Kaplan–Meier curves of progression-free survival (PFS) from the initiation of EVP stratified by pretreatment CAR (< 4.0 vs. ≥ 4.0).

Figure 4

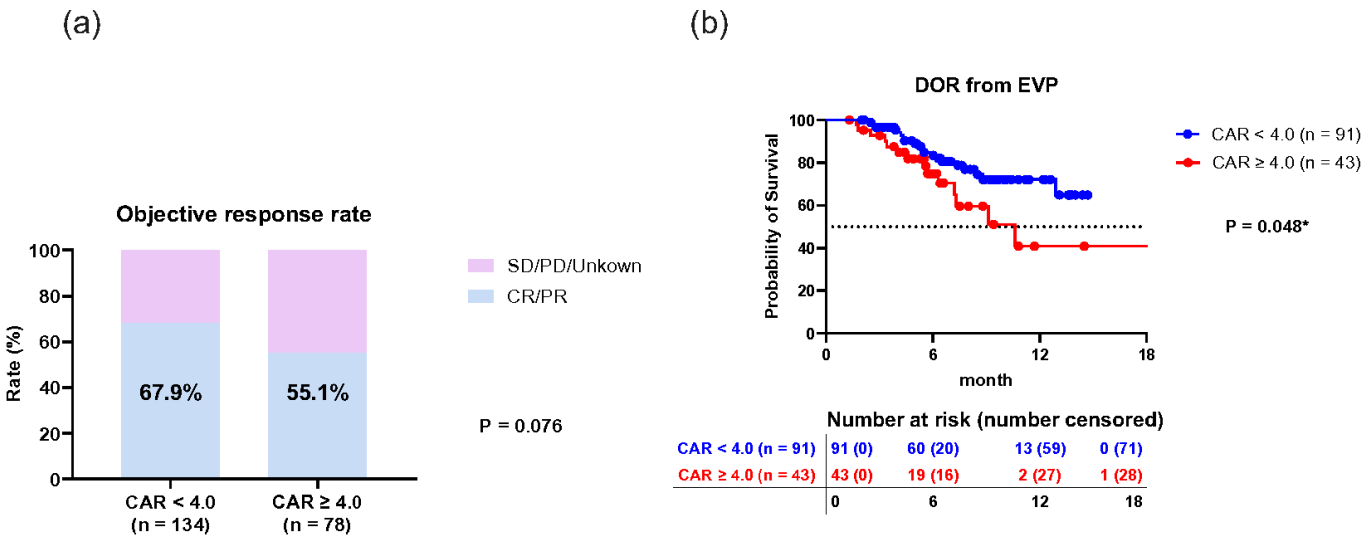


Figure 4

(a) Objective response rate (ORR) according to a cutoff value of 4.0 for the C-reactive protein-Albumin ratio (CAR). Objective response was defined as complete response (CR) or partial response (PR) according to RECIST v1.1.

(b) Kaplan–Meier curves of duration of response (DOR) from the initiation of enfortumab vedotin plus pembrolizumab (EVP) among responders according to a cutoff value of 4.0 for the CAR.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.pdf
- Table2.pdf