

Real-World Patterns of First-Line Treatment Selection After the Introduction of Enfortumab Vedotin Plus Pembrolizumab for Advanced Urothelial Carcinoma

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Table 1 is available in the Supplementary Files section.

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**Real-World Patterns of First-Line Treatment Selection After the Introduction of
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Running head: Real-World First-Line Treatment Selection in Ia/mUC

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Abstract

Background

The approval of enfortumab vedotin plus pembrolizumab (EVP) has substantially changed the first-line treatment landscape for locally advanced or metastatic urothelial carcinoma. However, little is known about how first-line treatment is selected in routine clinical practice following the introduction of EVP.

Methods

This multicenter retrospective study included 175 consecutive patients with untreated locally advanced or metastatic urothelial carcinoma who initiated first-line management after EVP approval between September 2024 and January 2026. Patients received EVP, gemcitabine plus cisplatin plus nivolumab (GCN), or non-EVP management, including

platinum-based chemotherapy, pembrolizumab monotherapy, supportive care only, or treatment refusal. Clinical factors associated with non-EVP selection were evaluated using receiver operating characteristic analyses, including area under the curve (AUC), multivariable logistic regression, decision curve analysis, and a nomogram. The EV-ineligible criteria (EVITA) were explored as a secondary assessment.

Results

Among 175 patients, 136 (78%) received EVP, 35 (20%) received non-EVP management, and four (2%) received GCN. Patients managed without EVP were substantially older and had poorer ECOG performance status than those receiving EVP. Age demonstrated the highest discriminative ability for non-EVP selection (AUC 0.85), followed by ECOG performance status (AUC 0.77), both outperforming EVITA (AUC 0.71). In multivariable analysis, older age and worse ECOG performance status were independently associated with non-EVP selection, whereas EVITA was not. Decision curve analysis showed that a model incorporating age and ECOG performance status achieved the greatest net benefit, and the addition of EVITA did not improve model performance. A nomogram based on age and ECOG performance status demonstrated excellent discrimination (AUC 0.87) and good internal calibration.

Conclusions

Following the introduction of EVP, first-line treatment selection in clinical practice was primarily associated with age and performance status. Simple clinical variables outperformed the composite EVITA criteria in describing real-world treatment selection, highlighting the gap between structured eligibility tools and contemporary clinical practice.

Keywords: Advanced urothelial carcinoma, Enfortumab vedotin plus pembrolizumab, First-line treatment, Real-world study, Treatment selection, Performance status

Introduction

The approval of enfortumab vedotin plus pembrolizumab (EVP) has fundamentally changed the first-line treatment landscape for patients with locally advanced or metastatic urothelial carcinoma (la/mUC) [1-5]. Compared with platinum-based chemotherapy, EVP has demonstrated substantial improvements in survival and antitumor activity, leading to its rapid incorporation into contemporary treatment guidelines [6-9] and clinical practice [10-14]. As a result, clinicians are increasingly required to determine which patients are appropriate candidates for EVP and which may be better managed with alternative strategies, including platinum-based chemotherapy, immune checkpoint inhibitor monotherapy, or supportive care.

Although EVP has become an important treatment option, patient selection remains challenging in routine practice. Older patients, those with impaired performance status, multiple comorbidities, or frailty are frequently underrepresented in pivotal clinical trials, yet represent a substantial proportion of patients encountered in daily practice [15-28]. Consequently, treatment decisions often rely on clinical judgment that balances potential therapeutic benefit against tolerability and patient preferences. However, little is known about how first-line treatment is actually selected following the introduction of EVP in real-world clinical settings.

Several tools have been proposed to support treatment decisions for EVP. The EV-

ineligible criteria (EVITA) were developed to identify patients at increased risk of EV-related toxicity using readily available baseline clinical variables [29] . However, EVITA was not originally designed to guide first-line treatment selection, and its role in contemporary clinical decision-making remains uncertain [30-34].

Therefore, we conducted a multicenter real-world study to characterize first-line treatment selection after the introduction of EVP and to identify clinical factors associated with management without EVP. We also explored whether EVITA provides additional information beyond basic clinical variables in describing treatment selection in routine practice.

Methods

Study design and ethics statement

This multicenter, retrospective observational study was conducted across participating institutions in Japan and included consecutive patients with la/mUC who initiated first-line management after the approval of EVP in routine clinical practice. The study period spanned from September 2024 to January 2026. Clinical data were extracted from institutional medical records using a standardized data collection form. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee of Hirosaki University School of Medicine and the ethics committees of all participating institutions (approval numbers: 2019-099-2 and 2021-158-2). Given the retrospective design and use of anonymized data, written informed consent was waived, and an opt-out consent procedure was applied.

Patient selection and clinical assessment

Consecutive patients with untreated la/mUC who initiated first-line management after the introduction of EVP between September 2024 and January 2026 were eligible. First-line management was categorized as EVP, gemcitabine plus cisplatin plus nivolumab (GCN), or non-EVP management. The non-EVP group included patients treated with platinum-based chemotherapy (GC/GCb), pembrolizumab monotherapy, supportive care only, and treatment-eligible patients who declined systemic therapy.

Baseline clinical characteristics included age, sex, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG PS), primary tumor site, TNM stage, renal function, hemoglobin, serum albumin, and other routinely available laboratory variables. Tumor stage was classified according to the eighth edition of the TNM classification.

The EV-ineligible criteria (EVITA) were evaluated as an exploratory composite assessment of baseline vulnerability. EVITA consists of five predefined clinical factors associated with EV-related toxicity: impaired renal function (estimated glomerular filtration rate <45 mL/min/1.73 m²), ECOG PS ≥ 2 , pre-existing grade ≥ 2 peripheral neuropathy, poorly controlled diabetes (HbA1c $\geq 8.0\%$), and baseline corneal or retinal abnormalities [29]. Patients were categorized according to the total EVITA score (0, 1, or ≥ 2).

Outcome measures

The primary objective was to characterize real-world first-line treatment selection following the introduction of EVP and to identify clinical factors associated with non-EVP management.

Receiver operating characteristic (ROC) analyses were performed to evaluate the discriminative ability of candidate clinical variables. Multivariable logistic regression, decision curve analysis (DCA), and nomogram development were used to assess factors associated with non-EVP management.

As an exploratory analysis, the EVITA score was evaluated to determine whether it provided additional information beyond simple clinical variables in describing real-world treatment selection. Short-term progression-free survival (PFS) and overall survival (OS) according to EVITA category were also descriptively assessed.

Statistical analysis

Categorical variables were compared using Fisher's exact test or the χ^2 test, and continuous variables using the Mann–Whitney U test. ROC analyses were performed to evaluate the ability of candidate clinical variables to identify patients managed without EVP. Multivariable logistic regression identified independent factors associated with non-EVP management. DCA evaluated the clinical usefulness of prediction models across clinically relevant threshold probabilities. A nomogram was developed based on the final multivariable model. Internal validation was performed using 1,000 bootstrap resamples. Model discrimination was assessed using the area under the ROC curve (AUC), calibration by calibration slope and intercept, and overall performance using the Brier score. Exploratory survival analyses were performed using the Kaplan–Meier method. A two-sided P value <0.05 was considered statistically significant.

Results

Patient characteristics and real-world treatment patterns

A total of 175 patients with previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC) who initiated first-line management following the introduction of EVP were included (**Fig. 1A**). First-line management consisted of EVP in 136 patients (78%), non-EVP management in 35 (20%), and gemcitabine plus cisplatin plus nivolumab (GCN) in four (2%). Among patients managed without EVP, 23 were considered eligible for systemic therapy and received platinum-based chemotherapy (GC/GCb, $n=11$), pembrolizumab monotherapy ($n=5$), or declined treatment despite eligibility ($n=7$), whereas 12 patients received supportive care only because of severe frailty, major comorbidities, or limited life expectancy (**Fig. 1B**).

Baseline characteristics are summarized in **Table 1**. Compared with patients treated with EVP, those managed without EVP were substantially older (median age 84 vs. 74 years, $P<0.001$) and more frequently had poor performance status (ECOG PS ≥ 2 : 57% vs. 12%, $P<0.001$). They also had lower body mass index (21 vs. 23 kg/m², $P=0.03$), lower hemoglobin (10 vs. 12 g/dL, $P=0.001$), lower serum albumin (3.2 vs. 3.7 g/dL, $P=0.004$), and poorer renal function (median eGFR 42 vs. 49 mL/min/1.73 m², $P=0.03$). Sex distribution and primary tumor site were comparable between groups.

Among clinically eligible patients managed without EVP, age remained significantly higher than in the EVP group (82 vs. 74 years, $P<0.001$), and ECOG PS ≥ 2 remained more frequent (39% vs. 12%, $P=0.003$). In contrast, differences in BMI, serum albumin, renal function, and primary tumor site were attenuated, whereas lower hemoglobin remained significant (10 vs. 12 g/dL, $P=0.007$).

Clinical factors associated with non-EVP selection

Receiver operating characteristic analyses were performed to evaluate clinical factors associated with selection of non-EVP management compared with EVP (**Fig. 2**). Among the candidate variables, age showed the highest discriminative ability for non-EVP selection, with an AUC of 0.85 (**Fig. 2A**). ECOG PS also demonstrated good discrimination (AUC 0.77; **Fig. 2B**), whereas EVITA showed moderate discrimination (AUC 0.71; **Fig. 2C**). Laboratory and anthropometric variables had lower discriminative performance, including hemoglobin (AUC 0.68; **Fig. 2D**), serum albumin (AUC 0.66; **Fig. 2E**), BMI (AUC 0.62; **Fig. 2F**), and eGFR (AUC 0.62; **Fig. 2G**).

In multivariable logistic regression including factors with AUC >0.70, older age (OR 1.21 per year; $P < 0.001$) and worse ECOG PS (OR 1.85 per category; $P = 0.01$) were independently associated with non-EVP selection. In contrast, EVITA was not independently associated with non-EVP selection after adjustment for age and ECOG PS (OR 1.10; $P = 0.9$) (**Fig. 2H**).

Clinical utility of prediction models

DCA was performed to compare the clinical utility of prediction models for non-EVP selection (**Fig. 3A**). Across clinically relevant threshold probabilities, the model incorporating age and ECOG PS consistently demonstrated the greatest net benefit. Adding EVITA to this model did not meaningfully improve performance, indicating little additional clinical value beyond these two readily available clinical variables.

To facilitate comparison, net benefit was summarized across threshold probabilities of 40–60% (**Fig. 3B**). The age + ECOG PS model achieved the highest net benefit (8.0%), which was comparable to that of the age + ECOG PS + EVITA model (7.8%). In contrast,

models based on age alone (6.8%), ECOG PS alone (4.5%), or EVITA alone (1.8%) showed progressively lower net benefit.

Prediction model for non-EVP selection

Based on the multivariable logistic regression model, a nomogram incorporating age and ECOG PS was developed to estimate the probability of non-EVP selection (**Fig. 4A**). The nomogram demonstrated excellent discriminative ability, with an AUC of 0.87 (**Fig. 4B**). Bootstrap internal validation confirmed good model performance, with minimal optimism (optimism-corrected AUC 0.87), a Brier score of 0.093, and good calibration (**Fig. S1**). To facilitate clinical interpretation, predicted probabilities of non-EVP selection were visualized across combinations of age and ECOG PS (**Fig. 4C**). The probability of non-EVP management increased progressively with advancing age and worsening ECOG PS, reaching more than 90% in the oldest patients with ECOG PS 3.

Exploratory analysis of EVITA according to treatment selection

As an exploratory analysis, the EVITA score was evaluated across treatment groups to examine its relationship with real-world treatment selection (**Fig. 5**). Median EVITA scores were significantly higher in patients receiving supportive care only than in those treated with EVP (median 1 vs. 0, $P<0.001$), whereas clinically eligible patients managed without EVP (GC/GCb, pembrolizumab monotherapy, or treatment refusal) also had higher scores than the EVP group (median 1 vs. 0, $P=0.01$) (**Fig. 5A**). Similarly, the proportion of patients with EVITA ≥ 2 was highest in the supportive care-only group (58%), followed by the clinically eligible non-EVP group (22%), compared with 6.6% among patients receiving EVP (**Fig. 5B**).

Analysis of individual EVITA components demonstrated that poor performance status (ECOG PS ≥ 2) accounted for most of the differences between treatment groups, whereas the remaining components were relatively uncommon (**Fig. 5C**). Patients managed without EVP were also substantially older than those receiving EVP, with median ages of 85 years in the supportive care-only group and 82 years in the clinically eligible non-EVP group, compared with 74 years in the EVP group (**Fig. 5D**).

Exploratory outcomes according to EVITA

Exploratory analyses evaluated short-term outcomes according to EVITA categories (**Fig. S2**). Among patients treated with EVP, the 1-year OS and PFS rates were 80% and 59%, respectively (**Fig. S2A**). When stratified by EVITA category, patients with EVITA 2 tended to have poorer PFS and OS than those with EVITA 0 or 1 (**Fig. S2B, C**). A similar trend was observed among patients managed without EVP, in whom higher EVITA scores were associated with worse OS (**Fig. S2D**). Given the limited sample size and short follow-up, these findings should be considered hypothesis-generating.

Discussion

The introduction of EVP has substantially expanded first-line treatment options for patients with advanced urothelial carcinoma. However, evidence regarding how these therapies are selected in routine clinical practice remains limited. In this multicenter real-world study conducted immediately after the introduction of EVP in Japan, nearly four-fifths of patients received EVP, whereas one-fifth were managed with alternative approaches, including platinum-based chemotherapy, pembrolizumab monotherapy, supportive care only, or treatment refusal. Patients managed without EVP were

consistently older and had poorer performance status than those receiving EVP, indicating that chronological age and functional status remain the principal factors influencing treatment selection in contemporary practice.

Our findings complement emerging real-world evidence demonstrating that EVP retains favorable effectiveness and manageable toxicity outside the clinical trial setting. Recent multicenter cohorts from North America and Asia have reported clinical outcomes broadly consistent with EV-302 despite inclusion of older patients and those with greater comorbidity burdens than in pivotal trials [25-27]. However, these studies primarily focused on treatment efficacy and safety after EVP initiation. In contrast, the present study addresses an earlier and clinically important question: how first-line treatment is selected following the introduction of EVP. To our knowledge, this is among the first multicenter studies to quantitatively characterize real-world treatment allocation after EVP became available.

Age demonstrated the highest discriminative ability for non-EVP selection, followed by ECOG performance status, and both remained independently associated with treatment allocation in multivariable analysis. These findings are clinically intuitive because chronological age and functional status are fundamental considerations when balancing the expected benefits and potential toxicities of intensive systemic therapy.

DCA further demonstrated that a model incorporating age and ECOG PS provided the greatest clinical utility for identifying patients managed without EVP. The addition of EVITA did not meaningfully improve model performance, suggesting that simple clinical variables adequately describe real-world treatment selection in most patients. Based on these findings, we developed a nomogram using only age and ECOG PS,

which showed excellent discrimination and good internal calibration. Although this model is not intended to recommend treatment, it provides a practical framework for describing current treatment allocation and may facilitate future comparisons of practice patterns across institutions and healthcare systems.

The EVITA score was evaluated as an exploratory composite assessment because it was originally developed to estimate the risk of EVP-related toxicity rather than to guide first-line treatment selection [29, 33, 34]. Although EVITA scores differed across treatment groups, much of this difference appeared to be driven by age and performance status. Accordingly, EVITA was not independently associated with treatment allocation after adjustment for these fundamental clinical variables. These findings suggest that, in routine clinical practice, clinicians primarily rely on readily available measures of patient fitness when selecting first-line treatment. Whether more comprehensive geriatric assessments provide additional value beyond age and performance status warrants further investigation.

Several limitations should be acknowledged. First, this was a retrospective observational study, and treatment allocation was not randomized, introducing the possibility of residual confounding. Second, the sample size of the non-EVP subgroup was relatively small, particularly for individual treatment categories, limiting statistical power for subgroup analyses. Third, the study should be interpreted as an evaluation of factors associated with non-EVP management versus EVP rather than a comprehensive comparison across all available first-line treatment options. Finally, the nomogram requires external validation before broader application in other clinical settings.

Conclusions

This multicenter real-world study provides one of the earliest descriptions of first-line treatment selection following the introduction of EVP for la/mUC. Although several clinical characteristics differed between treatment groups, age and performance status emerged as the dominant factors associated with non-EVP management. These findings provide a contemporary benchmark of treatment allocation in routine practice and may inform future studies evaluating treatment decision-making in the evolving therapeutic landscape of la/mUC.

Declarations

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Data availability: The datasets generated and/or analyzed during the current study are not publicly available due to regulation of data usage (we do not have consent from all patients to publish this data) but are available from the corresponding author on reasonable request.

Consent to Participate: Written informed consent was waived, and an opt-out approach was applied through public disclosure of study information.

Consent for Publication: All authors approved for the publication.

Author contribution: Shingo Hatakeyama had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concepts and design: Shingo Hatakeyama and Keita Ishimoto. Acquisition of data: Keita Ishimoto, Takuma Narita, Yuya Sekine, Masanao Shinohara, Naoki Fujita, Yohei Kawashima, Shintaro Narita, Shin Kobayashi, Noriyuki Abe, Jotaro Mikami, Hayato Yamamoto, Kazuyuki Numakura, Satoshi Sato, Tomonori Habuchi, Shingo Hatakeyama. Analysis and interpretation of data: Shingo Hatakeyama, Takuma Narita, and Keita Ishimoto. Drafting of the manuscript: Shingo Hatakeyama and Keita

Ishimoto. Critical revision of the manuscript for important intellectual content: Shingo Hatakeyama, Takuma Narita, and Keita Ishimoto. Statistical analysis: Shingo Hatakeyama. Administrative, technical, or material support: Shingo Hatakeyama. Study supervision: Chikara Ohyama.

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Figure legends

Figure 1: Overview of first-line treatment selection following the introduction of enfortumab vedotin plus pembrolizumab (EVP).

(A) Patient flow and classification of first-line treatment. Patients managed without EVP (non-EVP) were classified into platinum-based chemotherapy (GC/GCb), pembrolizumab monotherapy, treatment refusal despite eligibility, and supportive care only. (B) Distribution of first-line treatment selection in the overall cohort.

*, Treatment eligible but refusal due to patient preference.

**, Supportive care was selected in patients with ECOG performance status 4, severe cognitive impairment, severe comorbidities, and/or estimated life expectancy within 3 months.

Fig. 2: Clinical factors associated with non-EVP selection.

Receiver operating characteristic (ROC) analyses for age (A), ECOG performance status (B), EVITA (C), hemoglobin (D), albumin (E), body mass index (BMI) (F), and estimated glomerular filtration rate (eGFR) (G). (H) Multivariable logistic regression analysis evaluating independent factors associated with non-EVP selection.

Fig. 3: Clinical utility of prediction models for non-EVP selection.

(A) Decision curve analysis comparing models based on age, ECOG performance status, EVITA, and their combinations. (B) Net benefit across threshold probabilities of 40–60%.

Fig. 4: Nomogram for predicting non-EVP selection.

(A) Nomogram based on age and ECOG performance status. (B) Receiver operating characteristic curve of the nomogram. (C) Estimated probability of non-EVP selection according to age and ECOG performance status.

Fig. 5: Exploratory evaluation of EVITA according to first-line treatment selection.

(A) Comparison of EVITA scores among treatment groups. (B) Proportion of patients with $EVITA \geq 2$. (C) Distribution of individual EVITA components. (D) Age distribution according to treatment group.

Figure S1. Calibration plot for the nomogram incorporating age and ECOG PS.

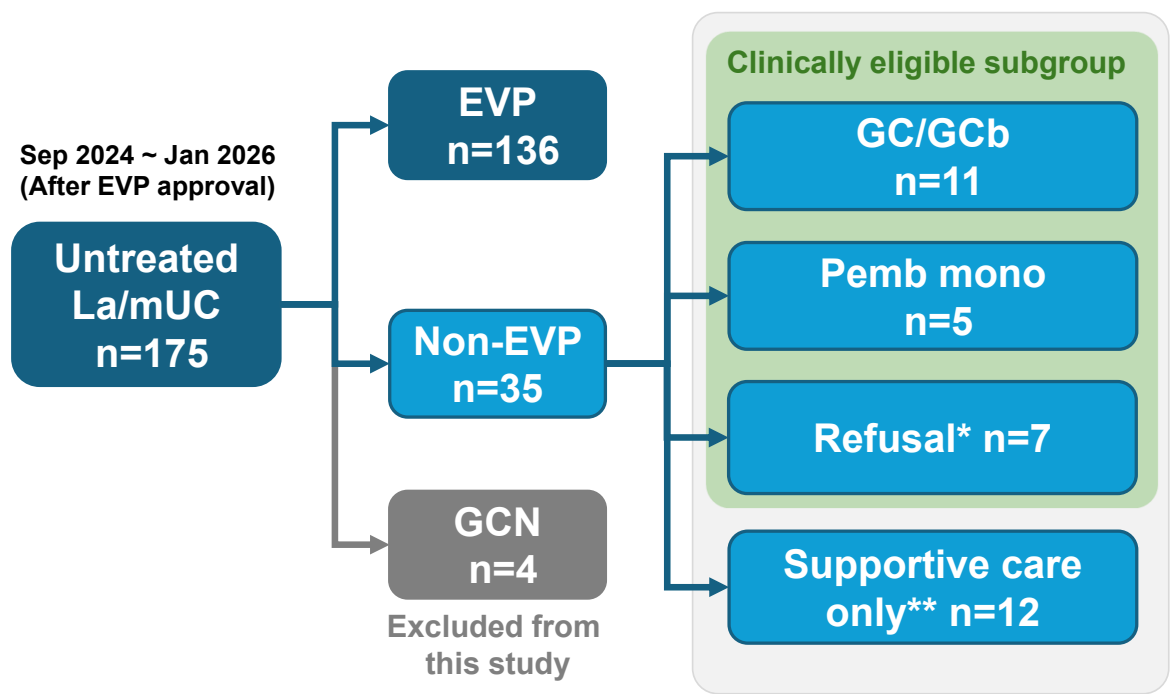
The calibration plot compares predicted probabilities of non-EVP selection with observed proportions. The dashed diagonal line represents perfect calibration. The solid line depicts the observed calibration across predicted risk groups. The plot demonstrates good agreement between predicted and observed probabilities, supporting acceptable internal calibration of the nomogram.

Figure S2. Exploratory clinical outcomes according to EVITA category.

(A) Overall survival (OS) and progression-free survival (PFS) in patients receiving EVP. (B) PFS according to EVITA category among patients receiving EVP. (C) OS according to EVITA category among patients receiving EVP. (D) OS according to EVITA category among patients managed without EVP.

Fig. 1

A



B

Distribution of First-Line selection

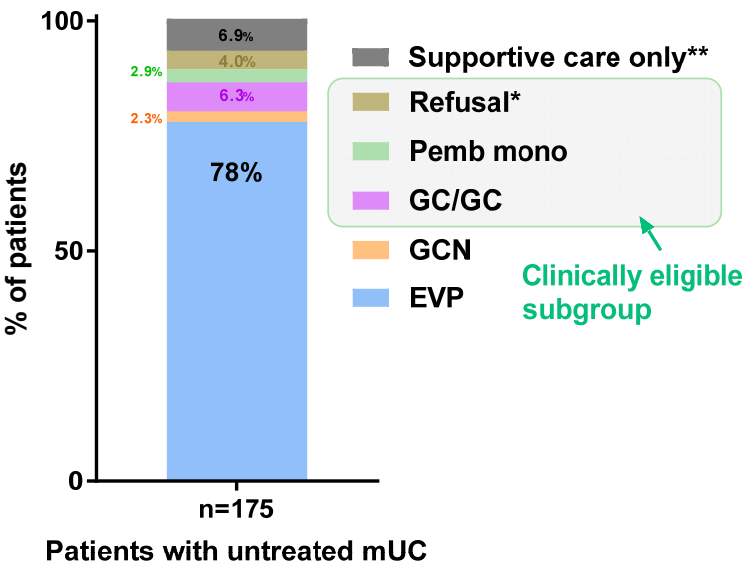


Fig. 2

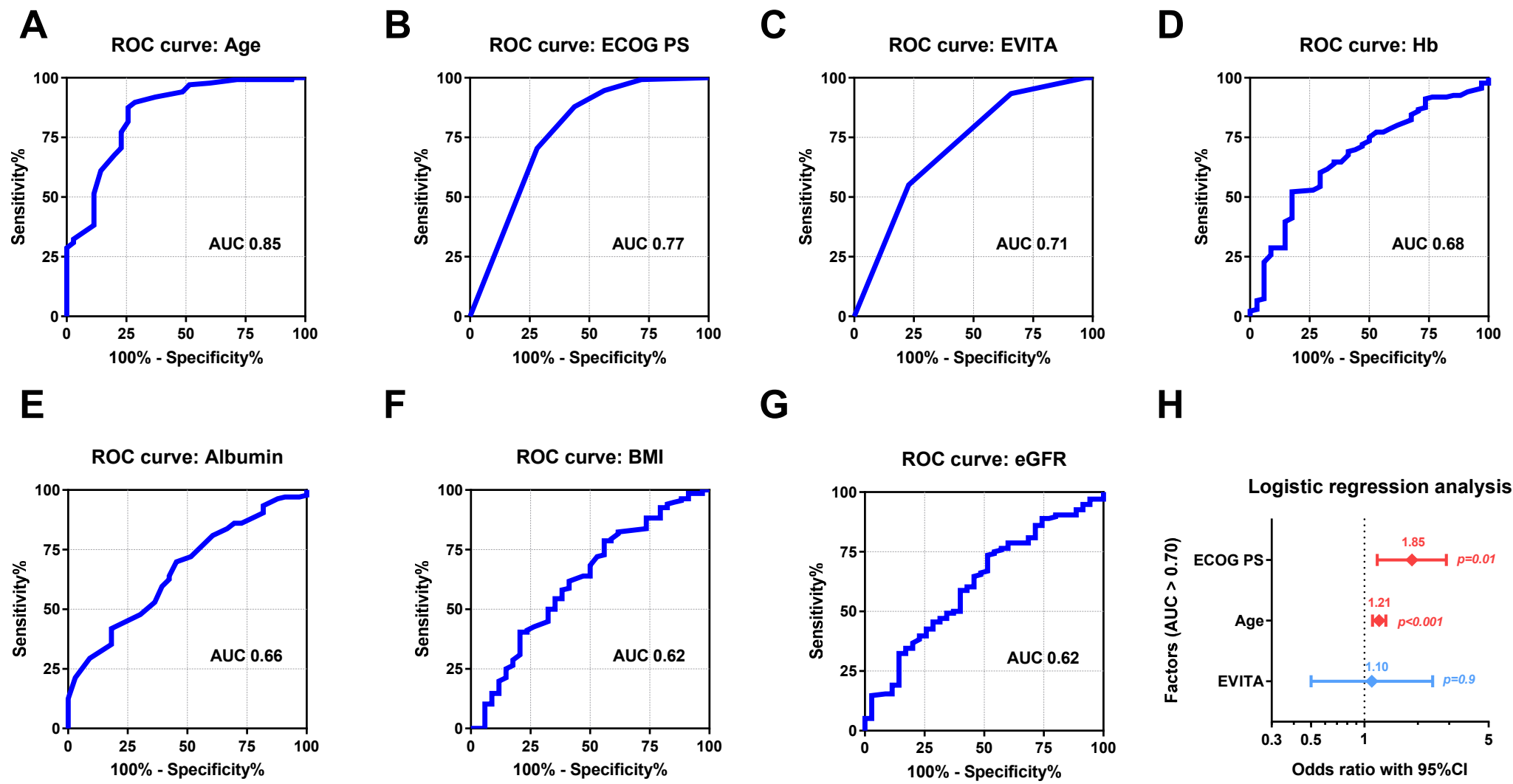
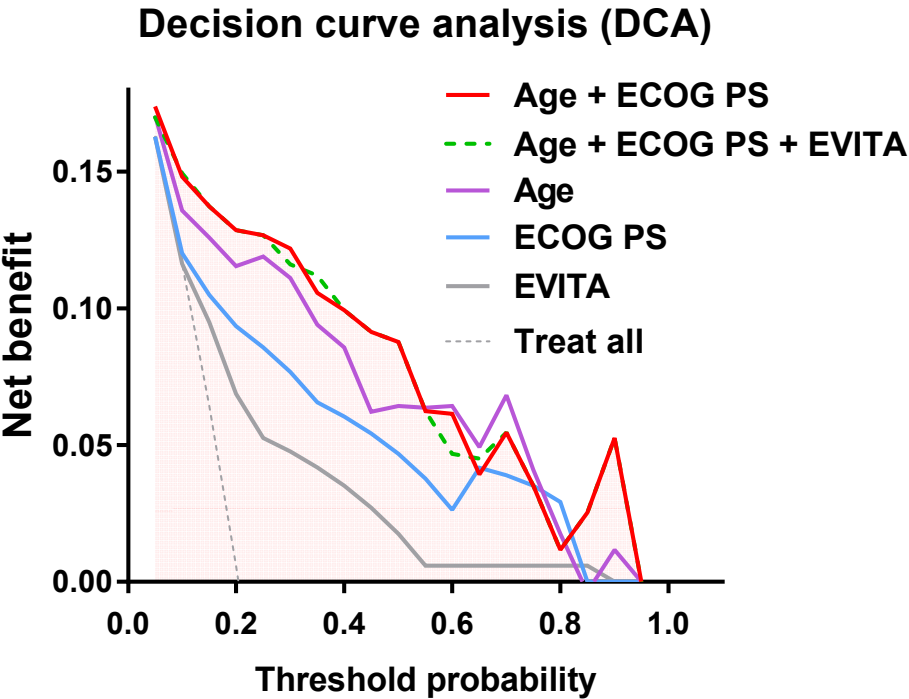


Fig. 3

A



B

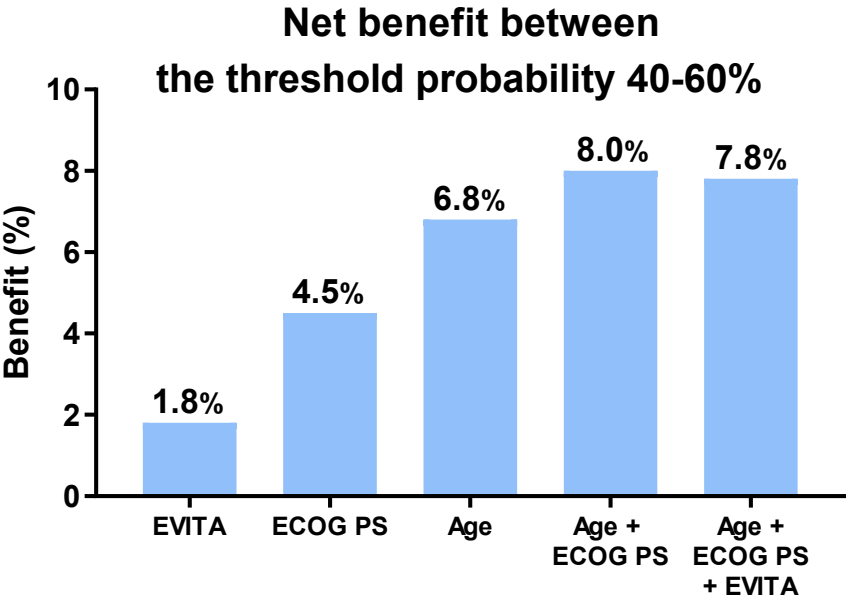
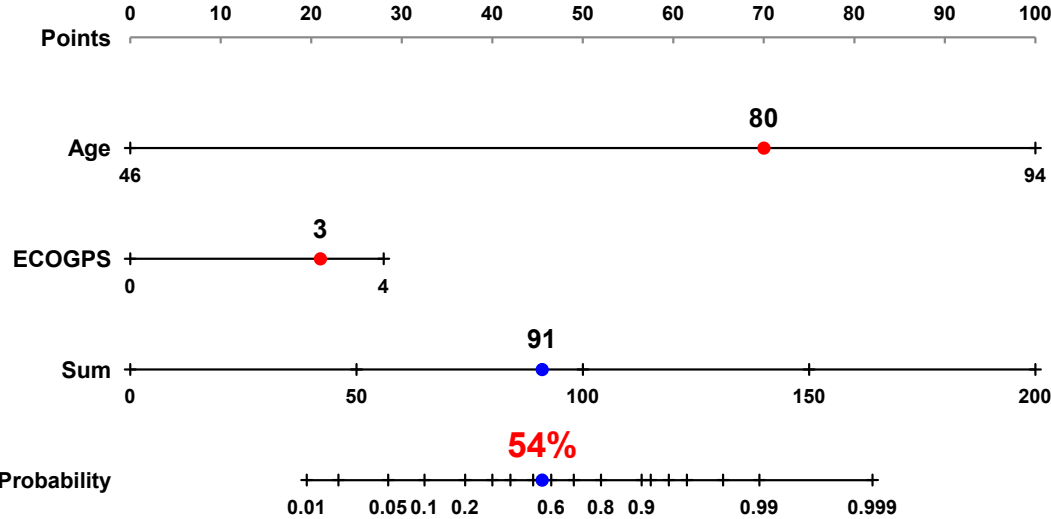


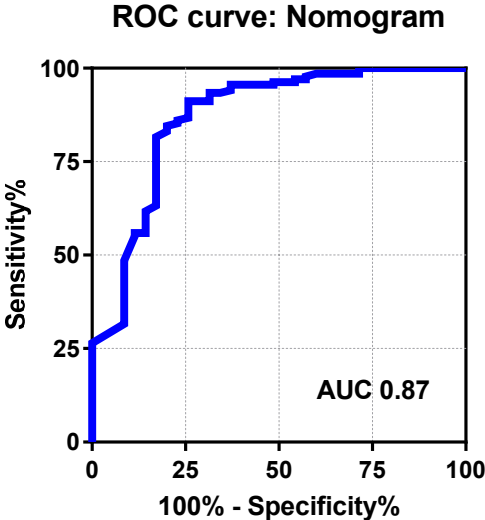
Fig. 4

A

Nomogram for non-EVP selection



B



C

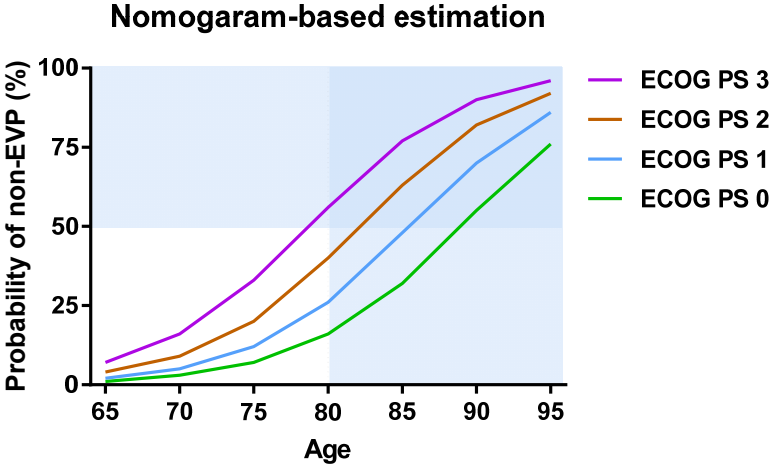
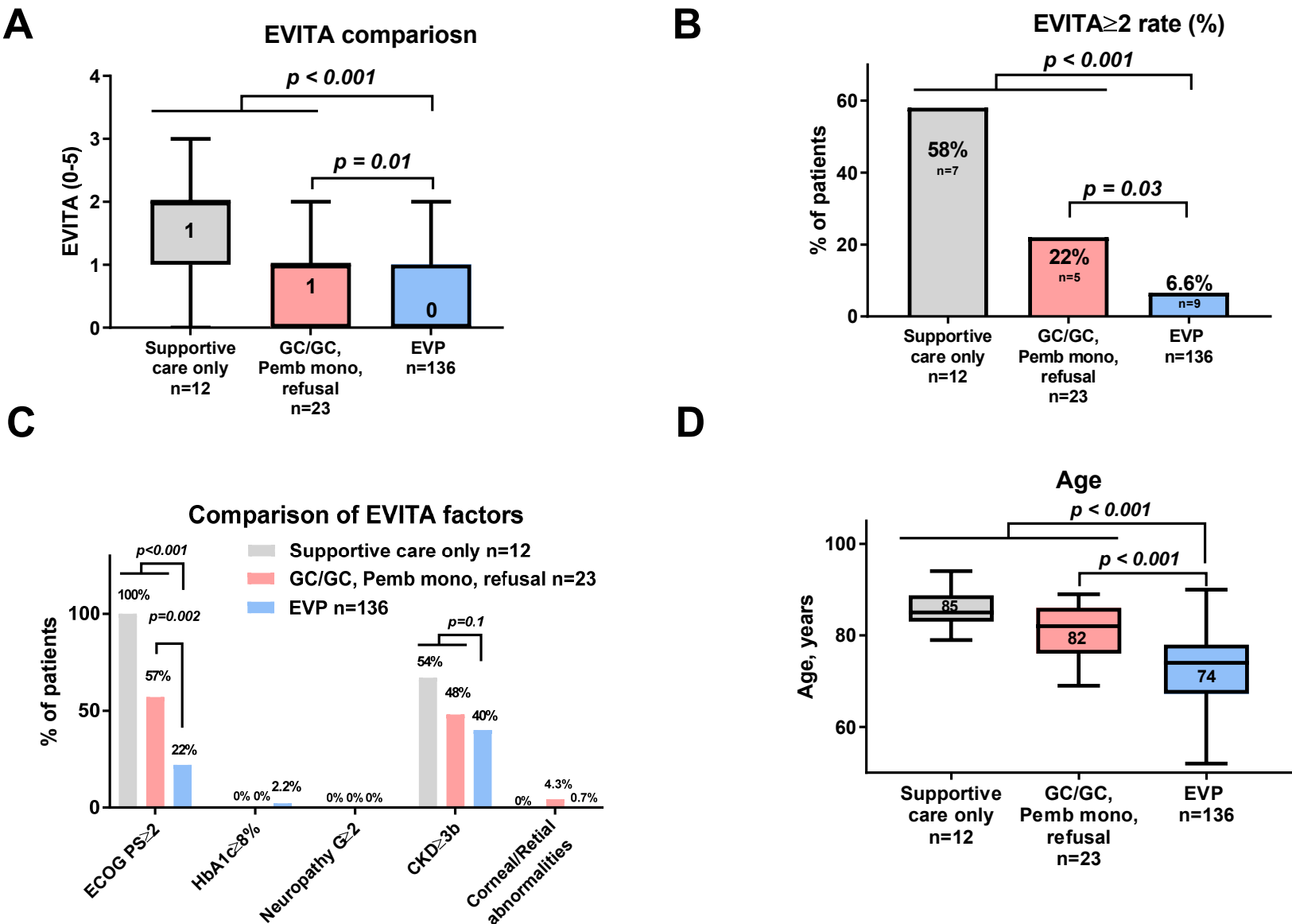


Fig. 5



Supplementary Files

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