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Original Article

Effects of nedaplatin combined with paclitaxel liposomes or docetaxel on survival rate and biomarkers in patients with recurrent ovarian cancer

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Abstract: Objectives: To investigate the effects of combining nedaplatin with paclitaxel liposomes or docetaxel on survival rates and biomarkers in patients with recurrent ovarian cancer (ROC). Methods: A retrospective analysis was carried out on the clinical data of 238 ROC patients treated at Baoji Traditional Chinese Medicine Hospital between February 2018 and February 2022. The patients were divided into a control group (n=103), which received nedaplatin combined with paclitaxel liposomes, and an observation group (n=135), receiving nedaplatin combined with docetaxel. The treatment efficacy, adverse reactions, tumor biomarkers (CA125, CEA, HE4, and AFP), and inflammatory markers (TNF-α, IL-6) before and after treatment were compared between the two groups. Patients were followed up for 2 years to observe progression-free survival (PFS), and Kaplan-Meier survival curves were plotted and Logrank tests were performed to evaluate the 2-year PFS differences. Results: There were no significant differences in overall clinical efficacy or remission rates between the two groups post-treatment (both P>0.05). Both groups showed significant reductions in tumor biomarkers and inflammatory markers after treatment compared with pre-treatment levels (all P<0.05), and the differences between the groups after treatment were not significant (all P>0.05). The incidence of adverse reactions was also similar between the groups (P>0.05). Multivariate Cox regression analysis identified the treatment regimen (P<0.001), FIGO stage (P=0.005), maximum diameter of recurrent lesions (P=0.001), number of recurrent lesions (P<0.001), post-treatment CA125 (P<0.001), and post-treatment HE4 (P<0.001) as independent prognostic factors for PFS. Conclusions: The combination of nedaplatin with paclitaxel liposomes or docetaxel demonstrated comparable efficacy in ROC patients, effectively reducing tumor and inflammatory markers without increasing adverse reactions. Importantly, the combination of nedaplatin and docetaxel significantly improved PFS.

Keywords: Nedaplatin, paclitaxel liposomes, docetaxel, recurrent ovarian cancer, progression-free survival, biomarkers

Introduction

Ovarian cancer (OC), ranking first in mortality among gynecological malignancies, is one of the most prevalent cancers in gynecology [1]. In 2018, around 22,240 new cases and 14,070 deaths were reported in the United States [2]. OC is marked by subtle initial symptoms and a lack of efficient screening techniques, resulting in approximately 75% of patients being diagnosed at advanced stages (III or IV), which poses challenges for early detection and intervention [3]. Due to the existence of standardized initial treatment protocols both domestically and internationally, a significant number of OC patients attain satisfactory outcomes after optimal cytoreductive surgery and standard combination chemotherapy, with some even achieving complete remission [4].

However, the recurrence rate of OC remains considerably high, with a recurrence risk ranging from 60% to 70%, and reaching up to 80%-

85% in patients with substantial residual lesions [5]. Recurrent OC (ROC) is currently incurable, mandating repeated treatments that take a toll on patients' quality of life and psychological well-being [6]. Hence, prolonging overall survival and progression-free survival (PFS) in ROC patients and enhancing their quality of life and mental state is of utmost importance [7]. Current treatment modalities for ROC encompass chemotherapy and secondary cytoreductive surgery (SCS) in conjunction with chemotherapy, yet there is no unified protocol [8]. Moreover, not all ROC patients are eligible for SCS; some, due to health status, surgical risks, postoperative recoveries, or financial constraints, may only choose chemotherapy [9]. Therefore, the pursuit of more personalized and efficacious treatment options to relieve suffering and upgrade quality of life remains a shared objective in the medical community and society at large.

Nedaplatin represents a novel platinum-based chemotherapeutic agent with relatively low toxicity and promising efficacy in specific cancer types [10]. Paclitaxel liposomes, an enhanced formulation of paclitaxel, augments drug stability and targeting through liposome encapsulation, thereby diminishing side effects [11]. Docetaxel is a widely employed chemotherapeutic drug for various solid tumors, known for its potent antitumor activity [12]. Although the combination of nedaplatin with either paclitaxel liposomes or docetaxel has shown potential in clinical settings, their effects and safety remain subjects of debate [13]. Different patients may exhibit varying responses to these treatments, and the associated adverse reactions warrant further investigation and assessment. Consequently, there are no unanimous conclusions or guidelines explicitly advocating these combination regimens for ROC treatment.

This study aims to explore the effects of nedaplatin in combination with paclitaxel liposomes or docetaxel on survival rates and biomarkers in ROC patients. By analyzing the alterations in PFS and biomarkers before and after treatment, this research aims to evaluate the efficacy and safety of these combined therapies, furnishing novel theoretical and clinical insights for individualized ROC treatment.

Methods and materials

Clinical data

A retrospective analysis was performed on the clinical data of 238 patients with recurrent ovarian cancer (ROC) treated at Baoji Traditional Chinese Medicine Hospital from February 2018 to February 2022. The inclusion criteria were as follows: (1) Patients had their initial diagnosis and treatment at this hospital, and all subsequent treatments after recurrence were also provided here. They received standardized initial treatment for ovarian cancer (OC). (2) Complete clinical records were accessible. (3) The estimated survival time was ≥3 months. (4) Patients had undergone secondary cytoreductive surgery (SCS) at the initial diagnosis but declined further SCS post-recurrence due to personal choice, financial limitations, or poor general health. (5) Patients were intolerant to conventional platinum-based chemotherapeutic agents like carboplatin or cisplatin. The exclusion criteria comprised: (1) A history of other malignant tumors. (2) Severe allergy to platinum drugs or other medications. (3) Bone marrow dysfunction. (4) Incomplete follow-up details. (5) Intolerance to drug treatment, leading to fewer than two completed treatment cycles. Patients were categorized into two groups according to the treatment protocol: a control group (n=103) receiving nedaplatin combined with paclitaxel liposomes, and an observation group (n=135) that received nedaplatin combined with docetaxel. Baseline data indicated no statistically significant differences between the two groups (P>0.05, **Table 1**). This study was approved by the Medical Ethics Committee of Baoji Traditional Chinese Medicine Hospital.

Treatment regimens

In the control group, on the first day of each treatment cycle, patients were administered paclitaxel liposomes (product number H2003-0357, 30 mg), manufactured by Nanjing Luye Pharmaceutical Co., Ltd. The dosage, ranging from 130 to 170 mg/m^2, was calculated based on the patient's body surface area. The paclitaxel liposome medication was diluted in 500 ml of 5% glucose solution and infused intravenously over 3 hours to guarantee smooth

Table 1. Comparison of baseline characteristics between the control group and observation group

Factor	Control Group (n=103)	Observation Group (n=135)	χ^2/Z Value	*P* Value
FIGO Stage				
I-II	33 (32.04%)	49 (36.3%)	0.469	0.493
III-IV	70 (67.96%)	86 (63.7%)		
Histological Grade				
Poorly Differentiated	16 (15.53%)	24 (17.78%)	0.801	0.67
Moderately Differentiated	47 (45.63%)	66 (48.89%)		
Well Differentiated	40 (38.83%)	45 (33.33%)		
Pathological Type				
Serous	69 (66.99%)	88 (65.19%)	0.236	0.889
Mucinous	13 (12.62%)	20 (14.81%)		
Others	21 (20.39%)	27 (20%)		
Residual Lesion after Initial Surgery				
Residual	37 (35.92%)	54 (40%)	0.411	0.521
No Residual	66 (64.08%)	81 (60%)		
Number of Recurrent Lesions				
1	38 (36.89%)	59 (43.7%)	1.122	0.289
>1	65 (63.11%)	76 (56.3%)		
Platinum Sensitivity				
Sensitive	51 (49.51%)	78 (57.78%)	1.607	0.205
Resistant	52 (50.49%)	57 (42.22%)		
Ascites				
Present	83 (80.58%)	119 (88.15%)	2.605	0.107
Absent	20 (19.42%)	16 (11.85%)		
Age	55.00 [49.50-61.50]	57.00 [51.00-64.00]	-1.517	0.129
Size of Residual Tumor Lesion	1.30 [0.60-2.00]	1.30 [0.55-1.80]	0.431	0.667
ECOG Score	2.00 [1.50-3.00]	2.00 [1.00-3.00]	1.02	0.28
Maximum Diameter of Recurrent Lesion	3.10 [1.90-3.90]	2.70 [1.45-3.80]	0.93	0.353

Note: FIGO, FIGO Staging; ECOG, Eastern Cooperative Oncology Group Performance Status.

absorption and distribution. Twenty-four hours after the paclitaxel liposome infusion, patients were given nedaplatin (product number H20051482, 20 mg), produced by Jilin Hengjin Pharmaceutical Co., Ltd., with a dosage range of 85 to 105 mg/m^2, mixed in 500 ml of 0.9% saline. The infusion duration was controlled to exceed 1 hour to ensure proper circulation and drug action. After the infusion, an additional 1500 to 2000 ml of 0.9% saline was administered to facilitate drug metabolism and minimize potential side effects.

In the observation group, on the first day of each treatment cycle, patients received docetaxel (product number H20198003, 20 mg), made by Guangdong Xinghao Pharmaceutical Co., Ltd., with a dosage range of 60 to 100 mg/m^2, dissolved in 500 ml of 5% glucose solution. In contrast to the control group, the intravenous infusion of docetaxel was completed swiftly within 30 minutes to attain a rapid therapeutic effect. On the second day, the nedaplatin treatment protocol was the same as that in the control group to maintain consistency in platinum drug application between the two groups. Both groups underwent treatment cycles of 3 weeks each. After each cycle, the medical staff conducted a comprehensive assessment of the patient's overall status and treatment efficacy. If the patient's condition deteriorated or if they exhibited intolerance to the treatment, the medical team promptly adjusted or discontinued the chemotherapy regimen to safeguard patient safety and well-being. Both groups received 2 to 6 cycles of chemotherapy.

Baseline data collection

Baseline data were collected from electronic medical records and included the following variables: age, FIGO stage (categorized as I+II and III+IV), histological grade (low, medium, and high differentiations), pathological type (serous, mucinous, and others), residual status after initial surgery (residual or no residual), size of residual tumor lesions (≥2 cm or <2 cm), ECOG score (scored 0-1 and 2), maximum diameter of recurrent lesions (≥4 cm or <4 cm), number of recurrent lesions, response to platinum drugs, presence of ascites, and incidence of adverse reactions.

Laboratory testing

Peripheral blood samples (5 ml) were drawn from patients one day before treatment (pre-treatment) and upon completion of the chemotherapy cycles (post-treatment). Serum was obtained after centrifugation, and tumor markers (AFP, CA125, CEA, and HE4) were measured using a Mindray fully automatic chemiluminescence immunoassay analyzer (CL-1200i). All reagents were supplied by the manufacturer. Inflammatory markers (TNF-α and IL-6) in serum were detected with enzyme-linked immunosorbent assay (ELISA) kits provided by Wuhan Triad Biotechnology Co., Ltd.

Efficacy evaluation and adverse reaction criteria

Following 2-6 cycles of treatment, efficacy evaluation was carried out in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [14]. Complete Response (CR): all physiological and biochemical parameters are normal, and all tumor cells are eliminated; Partial Response (PR): significant reduction in tumor size, with the sum of the maximum diameters reduced by more than half; Stable Disease (SD): effective control of tumor proliferation, with the sum of the maximum diameters reduced by less than half or increased by less than a quarter; Progressive Disease (PD): significant enlargement of tumor size, with the sum of the maximum diameters increased by at least a quarter. Adverse reactions were evaluated based on the World Health Organization (WHO) criteria for acute and subacute toxicity reactions of anticancer drugs [15].

Follow-up

All patients were followed up for 2 years. During the first year, follow-up examinations were conducted every 3 months; in the second year, they were carried out every 4 months. PFS was calculated from the end of the initial treatment for recurrence until disease progression, recurrence, or patient death, whichever occurred first.

Outcome measures

Primary outcome measures comprised the evaluation of differences in clinical efficacy after treatment, Cox regression analysis of independent prognostic factors affecting 2-year PFS, and the construction of Kaplan-Meier (K-M) survival curves for these prognostic factors.

Secondary outcome measures included the comparison of baseline data differences between the control and observation groups, the comparison of alterations in tumor markers and inflammatory markers before and after treatment between the two groups, the analysis of differences in these markers among patients with varying treatment efficacies, and the comparison of the incidence of adverse reactions in patients.

Statistical analysis

Data analysis was performed using R version 4.3.2, with various R packages utilized for different statistical analyses and visualization functions. Data preprocessing, such as filtering and grouping operations, was accomplished using the dplyr package. The ggplot2 package was utilized to generate assorted charts to visually depict data distribution and trends. The survival package was applied for Cox regression analysis and Kaplan-Meier survival curve plotting, while the survminer package enhanced the visualization of these survival curves. The car package was used for univariate analysis of variance and Tukey's HSD multiple comparison tests to compare differences between groups. The reshape2 package assisted in converting data from wide to long format for further analysis. The tableone package was utilized to generate baseline characteristic tables and perform chi-square tests for group comparisons. Finally, the broom package

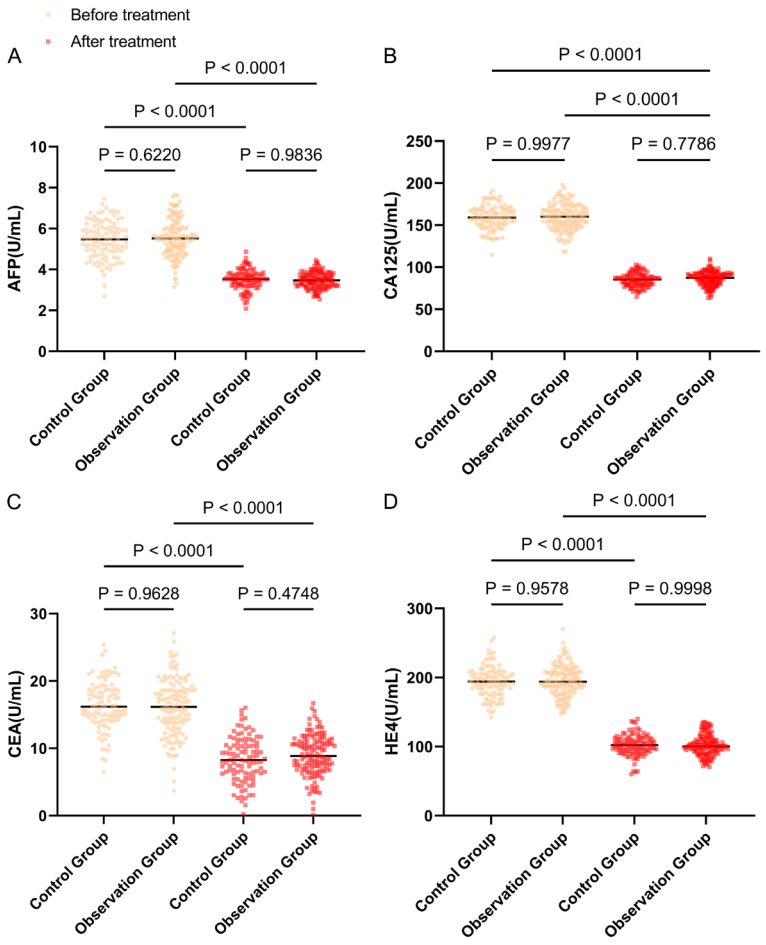

Figure 1. Comparative analysis of changes in tumor markers before and after treatment. A. AFP: Comparison of levels between the control group and the observation group before and after treatment; B. CA125: Changes in CA125 levels in both groups before and after treatment; C. CEA: Differences in CEA levels between the control group and the observation group before and after treatment; D. HE4: Changes in HE4 levels in both groups before and after treatment. Note: AFP, Alpha-Fetoprotein; CA125, Cancer Antigen 125; CEA, Carcinoembryonic Antigen; HE4, Human Epididymis Protein 4.

was used to tidy and enhance the presentation of regression analysis results, rendering them more interpretable and presentable. Statistical significance was set at P<0.05.

Results

Comparison of changes in tumor markers

In the comparison of tumor marker levels between the two groups, no statistically significant disparities were detected in the concentrations of AFP, CA125, CEA, and HE4 prior to treatment in the control and observation groups (all P>0.05, **Figure 1**). Following treatment, a pronounced decline in these tumor markers was witnessed in both groups (all P<0.001, **Figure 1**). Further comparative analysis revealed that, even subsequent to treatment, no statistically significant differences prevailed in the levels of AFP, CA125, CEA, and HE4 between the control and observation groups (all P>0.05, **Figure 1**).

Comparison of changes in TNF-α and IL-6

Regarding the comparison of TNF-α and IL-6 levels between the two groups, no statistically significant differences were observed in these inflammatory markers between the two groups before treatment (both P>0.05, **Figure 2**). After treatment, a significant decrease in TNF-α and IL-6 levels was noted in both groups, (both P<0.001, **Figure 2**), indicating the positive effect of the treatments in reducing inflammation. Further analysis after treatment showed that there were still no statistically significant differences in TNF-α and IL-6 levels between the control and observation groups (both P>0.05, **Figure 2**).

Comparison of clinical efficacy in patients

When contrasting the clinical efficacy of the treatments between the two groups, no statistically significant discrepancies were unearthed in terms of overall remission rates and overall treatment efficacy. Specifically, the *P*-value for the remission rate was 0.201, and the *P*-value for the overall efficacy was 0.268, both of which exceeded the significance threshold of 0.05 (**Figure 3**).

Comparison of adverse reactions

In the examination of the incidence of adverse reactions between the two groups, no statistically significant dissimilarities were identified with respect to hemoglobin reduction, leukopenia, thrombocytopenia, gastrointestinal reac-

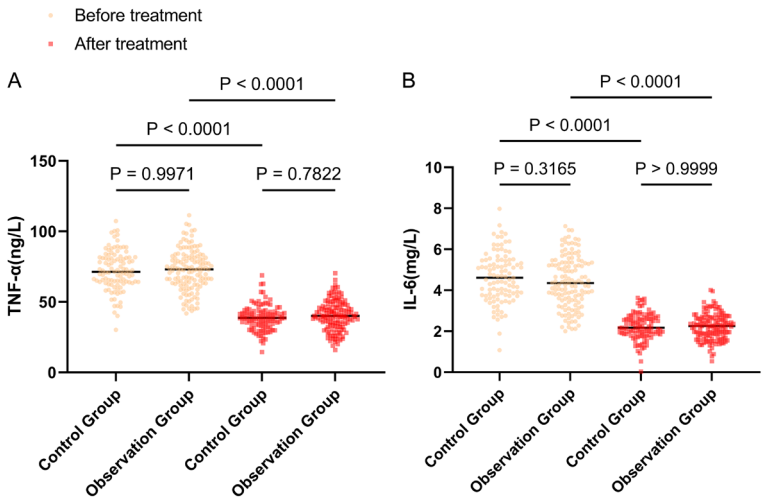

Figure 2. Comparative analysis of changes in inflammatory markers before and after treatment. A. TNF-α: Comparison of TNF-α levels between the control group and the observation group before and after treatment; B. IL-6: Changes in IL-6 levels in both groups before and after treatment. Note: TNF-α, Tumor Necrosis Factor Alpha; IL-6, Interleukin-6.

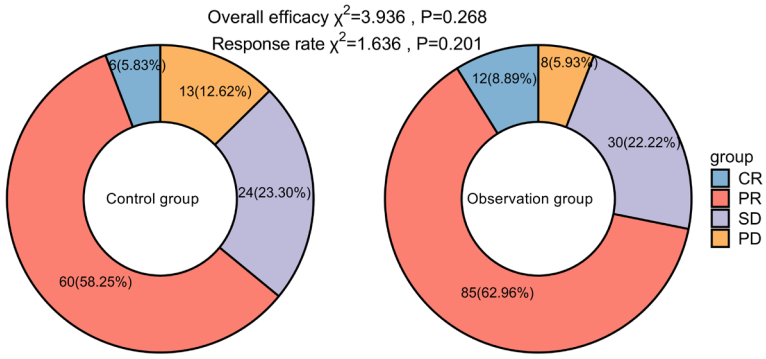

Figure 3. Clinical efficacy evaluation of the two groups of patients after treatment. Note: CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease.

tions, liver and kidney function impairment, and muscle pain (P>0.05, **Figure 4**).

Univariate cox regression analysis of prognostic factors for PFS

A 2-year follow-up was conducted for all 238 patients. During this tenure, 208 patients experienced PFS, yielding an incidence rate of 87.39%, with a median PFS time of 301 days. Cox regression analysis was conducted on the amassed data. Initially, data values were assigned (**Table 2**). Univariate analysis revealed that the treatment regimen (P=0.007, HR=1.469, 95% CI: 1.113-1.939), FIGO stage (P<0.001, HR=0.555, 95% CI: 0.413-0.747), histological grade (P<0.001, HR=0.614, 95% CI: 0.499-0.754), maximum diameter of recurrent lesions (P<0.001, HR=0.484, 95% CI: 0.351-0.668), number of recurrent lesions (P=0.004, HR=0.666, 95% CI: 0.503-0.88), post-treatment CA125 (U/mL) (P<0.001, HR=1.043, 95% CI: 1.026-1.06), and post-treatment HE4 (U/mL) (P<0.001, HR=1.029, 95% CI: 1.02-1.038) were potential prognostic factors affecting PFS (**Figure 5**).

Multivariate cox regression analysis of independent prognostic factors for PFS

Based on the results of the univariate Cox regression analysis, wherein seven prognostic factors were pinpointed, a multivariate Cox regression analysis was carried out to further evaluate their significance. For CA125 and HE4, X-tile software was employed to dichotomize the data, and the subsequent multivariate Cox regression was performed using the segmented data. The analysis confirmed that the treatment regimen (P<0.001, HR=2.319, 95% CI: 1.713-3.14), FIGO stage (P=0.005, HR=0.648, 95% CI: 0.478-0.878), histological grade (P=0.001, HR=0.673, 95% CI: 0.538-0.842), maximum diameter of recurrent lesions (P<0.001, HR=0.403, 95% CI: 0.289-0.561), number of recurrent lesions (P=0.001, HR=0.604, 95% CI: 0.453-0.804), post-treatment CA125 (U/mL) (P<0.001, HR=1.041, 95% CI: 1.023-1.06), and post-treatment HE4 (U/mL) (P<0.001, HR=1.021, 95% CI: 1.011-1.032) exerted significant influences on PFS (**Figure 6**).

Interaction analysis between treatment regimen and prognostic factors

Interaction analysis disclosed significant interactions between the treatment regimen and multiple prognostic factors, namely FIGO stage (P=0.037), histological grade (P<0.001), maxi-

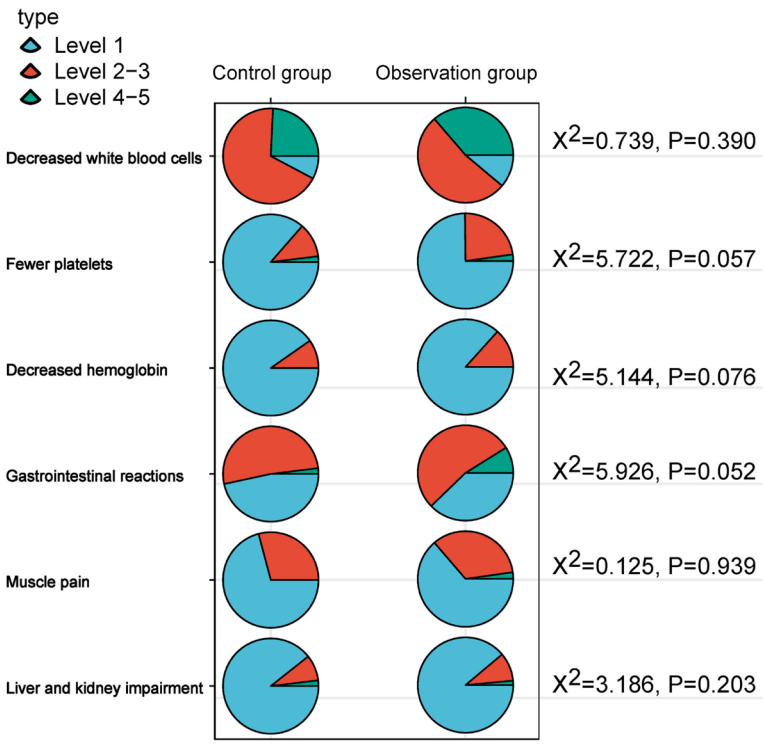

Figure 4. Visualization of adverse reactions in patients. Hemoglobin reduction: Control group 0 grade in 93 cases, 2-3 grade in 10 cases; observation group 0 grade in 107 cases, 2-3 grade in 28 cases. Leukopenia: Control group 0 grade in 8 cases, 2-3 grade in 70 cases, 4-5 grade in 25 cases; observation group 0 grade in 15 cases, 2-3 grade in 71 cases, 4-5 grade in 49 cases. Thrombocytopenia: Control group 0 grade in 89 cases, 2-3 grade in 12 cases, 4-5 grade in 2 cases; observation group 0 grade in 101 cases, 2-3 grade in 31 cases, 4-5 grade in 3 cases. Gastrointestinal reactions: Control group 0 grade in 48 cases, 2-3 grade in 53 cases, 4-5 grade in 2 cases; observation group 0 grade in 43 cases, 2-3 grade in 80 cases, 4-5 grade in 12 cases. Liver and kidney function damage: Control group 0 grade in 92 cases, 2-3 grade in 9 cases, 4-5 grade in 2 cases; observation group 0 grade in 120 cases, 2-3 grade in 13 cases, 4-5 grade in 2 cases. Muscle pain: Control group 0 grade in 73 cases, 2-3 grade in 30 cases; observation group 0 grade in 86 cases, 2-3 grade in 46 cases, 4-5 grade in 3 cases.

mum diameter of recurrent lesions (P<0.001), number of recurrent lesions (P=0.002), post-treatment CA125 (P<0.001), and post-treatment HE4 (P<0.001). These interactions suggest that treatment outcomes may vary in accordance with the specific characteristics of patients (**Figure 7**; **Table 3**).

Mediation analysis of treatment regimen and prognostic factors

Mediation analysis indicated that the investigated factors did not display significant mediation effects. The detailed outcomes were as follows: for FIGO stage, ACME was -0.0170 (P=0.34), ADE was 0.0906 (P=0.30); for histological grade, ACME was 0.0251 (P=0.28), ADE was 0.0528 (P=0.50); for the maximum diameter of recurrent lesions, ACME was 0.0125 (P=0.38), ADE was 0.0753 (P=0.40); for the number of recurrent lesions, ACME was -0.0114 (P=0.38), ADE was 0.0813 (P=0.46); for post-treatment CA125 level, ACME was 0.0439 (P=0.26), ADE was 0.0282 (P=0.78); for post-treatment HE4 level, ACME was -0.0342 (P=0.46), ADE was 0.1042 (P=0.24). These results suggest that the direct impact of the treatment regimen on survival was not significantly mediated by FIGO stage, histological grade, maximum diameter of recurrent lesions, number of recurrent lesions, post-treatment CA125 level, or post-treatment HE4 level (**Figure 8**).

Discussion

The treatment of OC has progressed significantly with the standardization of protocols and advances in ovarian biology research and diagnostic methods, leading to improved initial remission rates [16]. However, the prognosis for OC remains challenging due to chemotherapy resistance and a high recurrence rate. This study retrospectively analyzed 238 patients with ROC to compare the therapeutic effects of nedaplatin combined with paclitaxel liposomes versus docetaxel. The results demonstrated that both regimens effectively controlled the disease and yielded similar therapeutic outcomes, suggesting their viability as interchangeable treatment options in clinical practice. These findings align with Zhao et al.'s observations [17], which reported no significant differences in remission rates or adverse events among patients undergoing neoadjuvant therapy with paclitaxel, docetaxel, or liposomal paclitaxel.

Table 2. Assignment table

Factor	Assignment Content
Treatment Regimen	Control Group =1, Observation Group =0
Age (years)	<50=0, 50-60=1, >60=2
FIGO Stage	I-II =1, III-IV =0
Histological Grade	Poorly Differentiated =0, Moderately Differentiated =1, Well Differentiated =2
Pathological Type	Serous =0, Mucinous =1, Others =2
Residual Lesion after Initial Surgery	Residual =1, No Residual =0
Size of Residual Tumor Lesion	≥2 cm =1, <2 cm =0
ECOG Score	0-1=1, ≥2=0
Maximum Diameter of Recurrent Lesion	<4 cm =1, ≥4 cm =0
Number of Recurrent Lesions	1=1, >1=0
Platinum Sensitivity	Sensitive =1, Resistant =0
Ascites	Present =1, Absent =0
Post-treatment AFP (U/L)	Analyzed as a continuous variable using the original value
Post-treatment CA125 (U/mL)	Analyzed as a continuous variable using the original value
Post-treatment CEA (U/mL)	Analyzed as a continuous variable using the original value
Post-treatment HE4 (U/mL)	Analyzed as a continuous variable using the original value
Post-treatment TNF-α (ng/L)	Analyzed as a continuous variable using the original value
Post-treatment IL-6 (mg/L)	Analyzed as a continuous variable using the original value

Note: FIGO, FIGO Staging; ECOG, Eastern Cooperative Oncology Group Performance Status; AFP, Alpha-Fetoprotein; CA125, Cancer Antigen 125; CEA, Carcinoembryonic Antigen; HE4, Human Epididymis Protein 4; TNF-α, Tumor Necrosis Factor Alpha; IL-6, Interleukin-6.

Both treatment regimens significantly reduced tumor markers (AFP, CA125, CEA, HE4) and inflammatory factors (TNF-α, IL-6), although there were no significant differences between the two groups. This consistency in efficacy indicates that both regimens similarly influence these biomarkers. Su et al. [18] previously reported that HE4 levels significantly decreased following carboplatin combined with paclitaxel-based intraperitoneal hyperthermic chemotherapy in advanced ROC patients. Furthermore, Pelissier et al. [19] suggested that decreases in CA125 during neoadjuvant chemotherapy could predict platinum sensitivity and treatment efficacy, while Sanna et al. [20] identified a correlation between IL-6 levels after chemotherapy and clinical response. In our study, multivariate Cox regression analysis revealed that PFS was significantly associated with post-treatment CA125 and HE4 levels, suggesting that while short-term efficacy on these markers was similar for both regimens, their post-treatment levels may serve as predictors of long-term prognosis. These findings underscore the potential of these regimens in reducing tumor activity and inflammation. Both regimens exhibited comparable safety profiles, with no significant differences in adverse reactions, further supporting their clinical applicability.

Prognostic analysis identified several independent factors affecting PFS, including treatment regimen, FIGO stage, maximum diameter of recurrent lesions, number of recurrent lesions, post-treatment CA125, and post-treatment HE4 levels. These factors reflect disease severity and treatment responsiveness. Differences in patient responses to nedaplatin combined with paclitaxel liposome versus docetaxel may be attributed to variations in drug metabolism, distribution, and tumor-specific effects [21]. For example, Yang et al. [22] found no significant differences in 5-year overall survival between the two regimens, although PFS was higher in the docetaxel group, emphasizing the importance of selecting appropriate treatment regimens to optimize PFS.

FIGO staging remains a critical indicator of OC severity, with advanced-stage patients exhibiting poorer prognoses due to higher tumor burdens and more extensive dissemination [23]. Studies have consistently shown that patients with lower FIGO stages (I-II) achieve higher PFS and overall survival rates compared to those with advanced stages (III-IV) [24-26]. Similarly, the maximum diameter of recurrent lesions serves as an indicator of disease severity, with larger lesions often associated with greater tumor burden and reduced treatment efficacy

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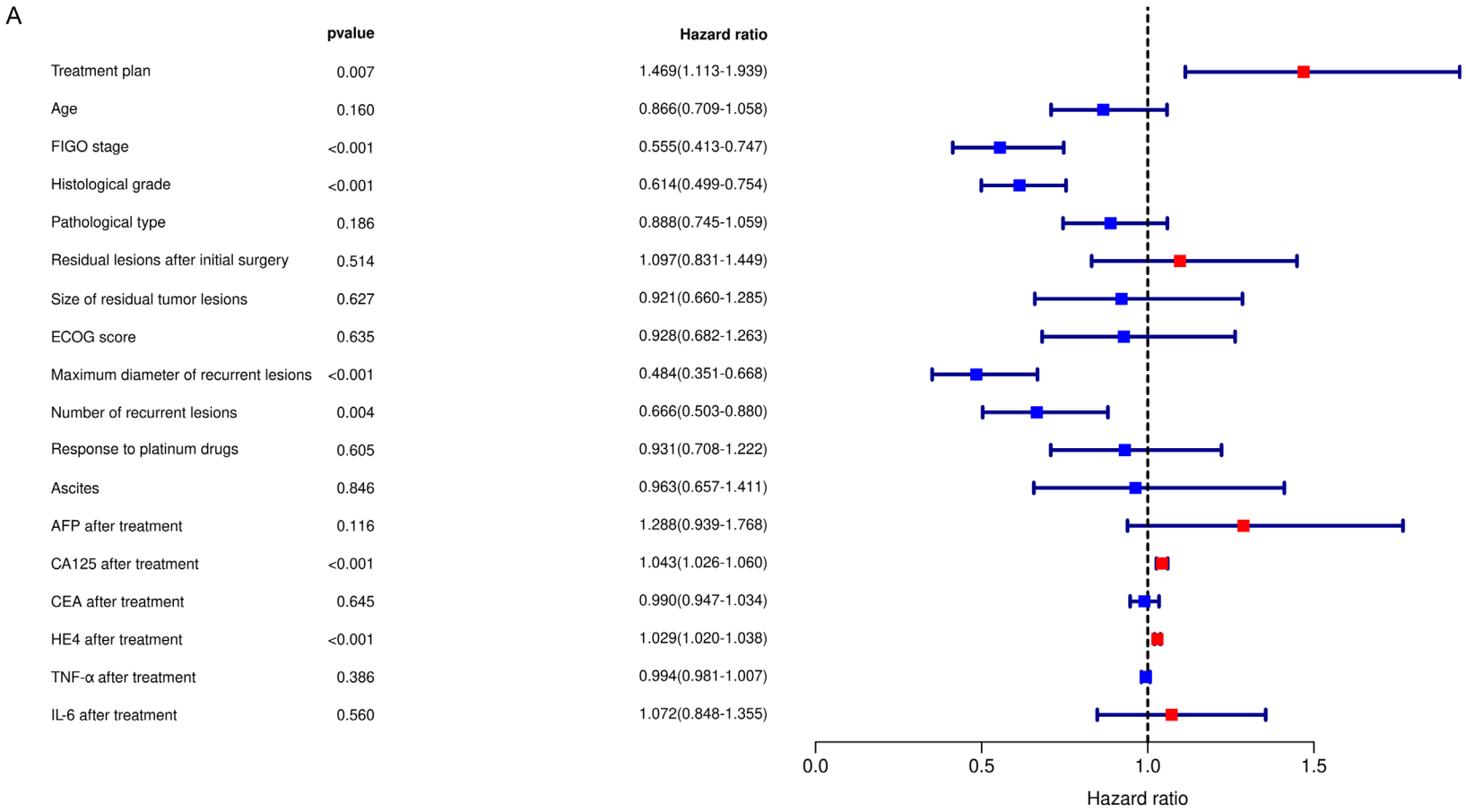
pvalue
Hazard ratio
Treatment plan 0.007 1.469(1.113-1.939)
Age 0.160 0.866(0.709-1.058)
FIGO stage <0.001 0.555(0.413-0.747)
Histological grade <0.001 0.614(0.499-0.754)
Pathological type 0.186 0.888(0.745-1.059)
Residual lesions after initial surgery 0.514 1.097(0.831-1.449)
Size of residual tumor lesions 0.627 0.921(0.660-1.285)
ECOG score 0.635 0.928(0.682-1.263)
Maximum diameter of recurrent lesions <0.001 0.484(0.351-0.668)
Number of recurrent lesions 0.004 0.666(0.503-0.880)
Response to platinum drugs 0.605 0.931(0.708-1.222)
Ascites 0.846 0.963(0.657-1.411)
AFP after treatment 0.116 1.288(0.939-1.768)
CA125 after treatment <0.001 1.043(1.026-1.060)
CEA after treatment 0.645 0.990(0.947-1.034)
HE4 after treatment <0.001 1.029(1.020-1.038)
TNF-α after treatment 0.386 0.994(0.981-1.007)
IL-6 after treatment 0.560 1.072(0.848-1.355)
0.0
0.5
1.0
1.5
Hazard ratio

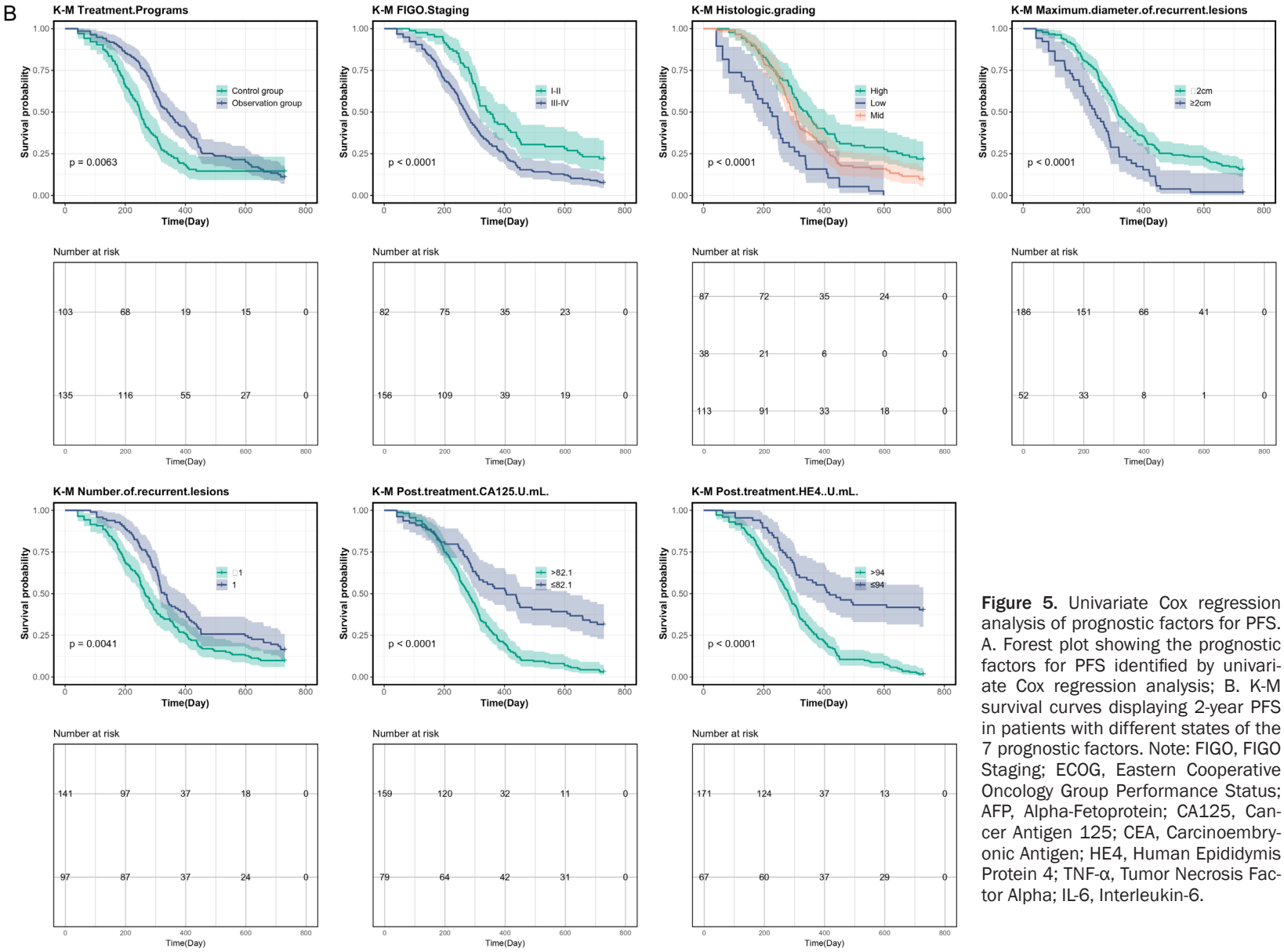

Figure 5. Univariate Cox regression analysis of prognostic factors for PFS. A. Forest plot showing the prognostic factors for PFS identified by univariate Cox regression analysis; B. K-M survival curves displaying 2-year PFS in patients with different states of the 7 prognostic factors. Note: FIGO, FIGO Staging; ECOG, Eastern Cooperative Oncology Group Performance Status; AFP, Alpha-Fetoprotein; CA125, Cancer Antigen 125; CEA, Carcinoembryonic Antigen; HE4, Human Epididymis Protein 4; TNF-α, Tumor Necrosis Factor Alpha; IL-6, Interleukin-6.

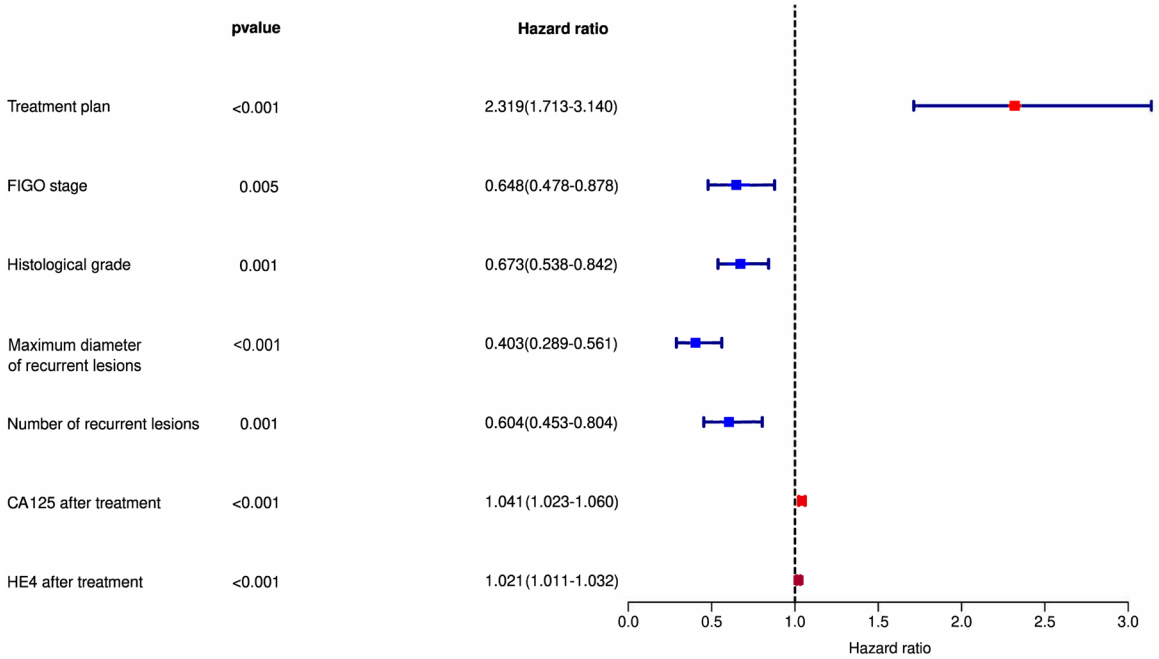

Figure 6. Multivariate Cox regression analysis identifying independent prognostic factors affecting PFS in recurrent patients. Note: FIGO, FIGO Staging; CA125, Cancer Antigen 125; HE4, Human Epididymis Protein 4.

[27]. Multiple recurrent lesions further complicate treatment, necessitating more extensive interventions and increasing uncertainty in outcomes [28, 29].

Tumor markers, particularly CA125 and HE4, play an essential role in monitoring disease progression and treatment response. Significant reductions in post-treatment CA125 levels typically indicate reduced tumor burden and positive treatment responses, though controversies remain [30]. For instance, Liang et al. [31] proposed that CA125 normalization before neoadjuvant chemotherapy predicts recurrence risk after initial treatment. Zeng et al. [32] suggested that reductions in CA125 during neoadjuvant chemotherapy are indicative of successful cytoreduction to no visible residual disease in advanced epithelial OC. Similarly, Li et al. [33] reported that paclitaxel combined with nedaplatin significantly reduced CA125 levels and extended PFS. HE4, another valuable marker, often increases before clinical symptoms appear, making it useful for early recurrence detection. Post-treatment reductions in HE4 are associated with lower recurrence risk and extended PFS [34]. These findings emphasize the importance of monitoring these markers to inform prognosis and treatment strategies.

Interaction analysis revealed significant interactions between treatment regimen and factors such as FIGO stage, histological grade, maximum diameter of recurrent lesions, number of recurrent lesions, and post-treatment CA125 and HE4 levels. These interactions suggest that treatment efficacy may vary depending on individual patient characteristics, such as tumor biology and health status. For example, patients with different FIGO stages or histological grades may respond differently to the same regimen. Similarly, tumor size and the number of recurrent lesions may influence treatment efficacy, while post-treatment levels of CA125 and HE4 likely reflect differences in tumor behavior and patient response. However, mediation analysis showed that these factors did not significantly mediate the relationship between treatment and survival, suggesting that the direct impact of the treatment regimen on survival is strong enough to overshadow potential mediation effects. Unmeasured factors, such as genetic variability or tumor microenvironment changes, may play more critical roles in influencing survival outcomes. These

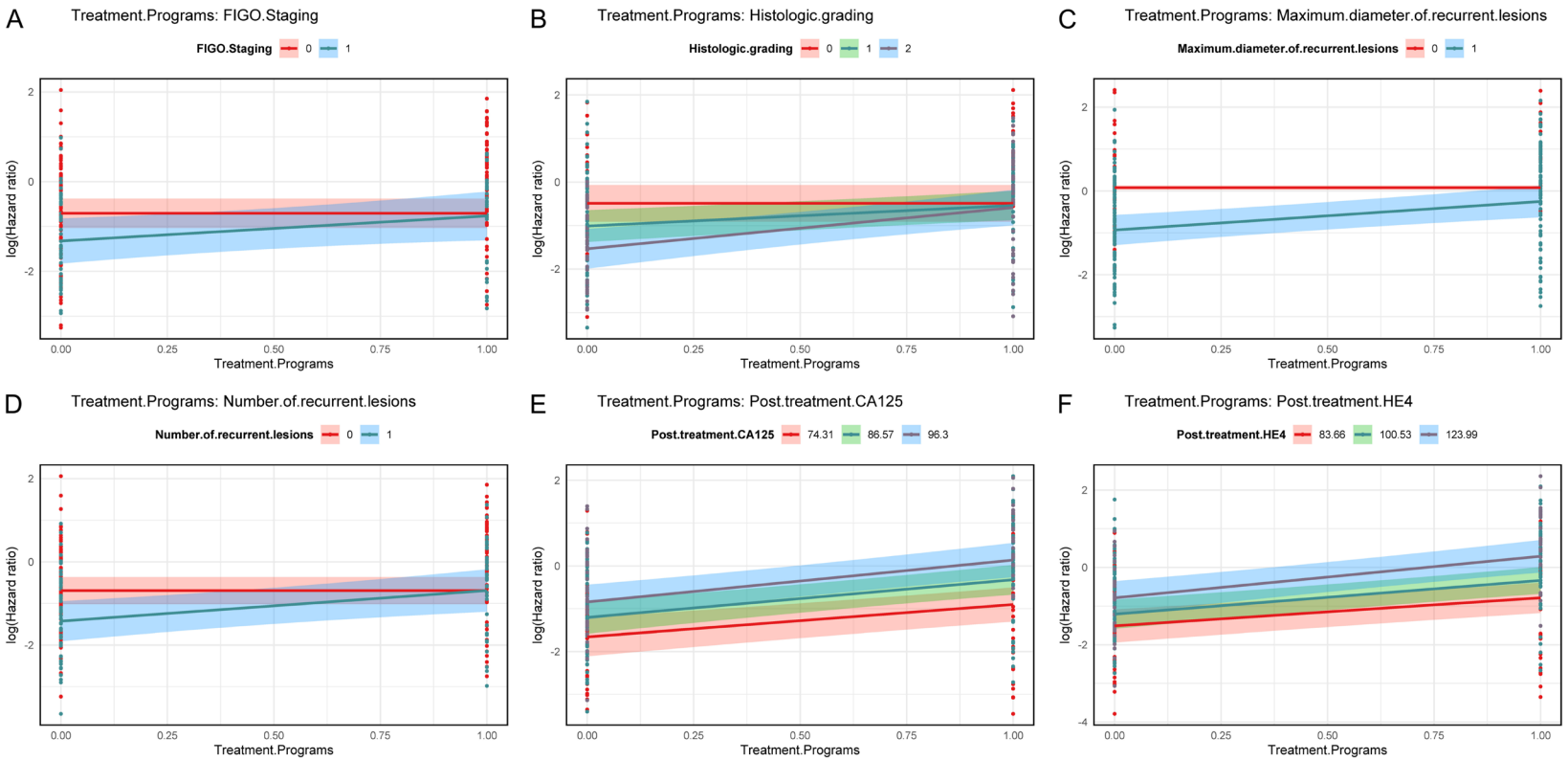

Figure 7. Interaction analysis of treatment regimens and other prognostic factors based on Cox regression model. A. Visual analysis of interaction between treatment regimen and FIGO Staging; B. Visual analysis of interaction between treatment regimen and Histologic grading; C. Visual analysis of interaction between treatment regimen and Maximum diameter of recurrent lesions; D. Visual analysis of interaction between treatment regimen and Number of recurrent lesions; E. Visual analysis of interaction between treatment regimen and Post treatment CA125; F. Visual analysis of interaction between treatment regimen and Post treatment HE4. Note: FIGO, FIGO Staging; CA125, Cancer Antigen 125; HE4, Human Epididymis Protein 4.

Table 3. Interaction parameters between treatment regimen and other prognostic factors

Index comparison	Coefficient	Exp Coefficient	Std Error	z value	*P* value
FIGO Staging vs Treatment Programs	0.559	1.749	1.749	0.268	0.037
Histologic grading vs Treatment Programs	0.474	1.606	1.606	0.112	<0.001
Maximum diameter of recurrent lesions vs Treatment Programs	0.683	1.979	1.979	0.171	<0.001
Number of recurrent lesions vs Treatment Programs	0.736	2.088	2.088	0.241	0.002
Post treatment CA125 vs Treatment Programs	0.010	1.010	1.010	0.002	<0.001
Post treatment HE4 vs Treatment Programs	0.009	1.009	1.009	0.001	<0.001

Note: FIGO, FIGO Staging; CA125, Cancer Antigen 125; HE4, Human Epididymis Protein 4.

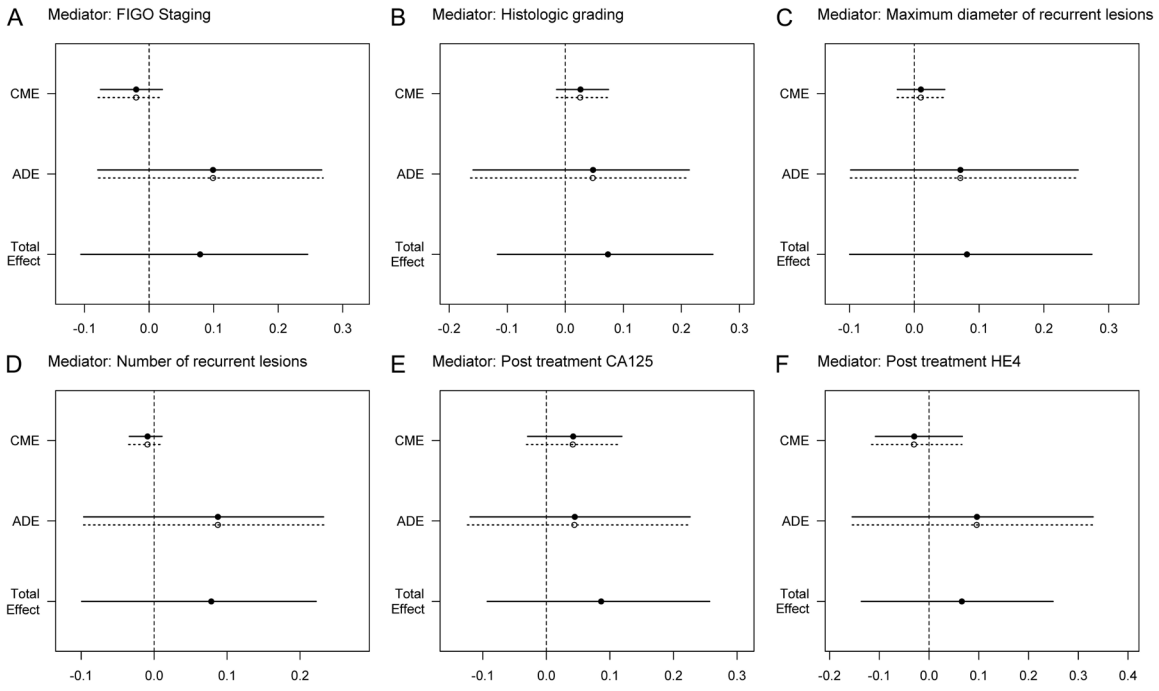

Figure 8. Analysis of mediation effects of treatment regimen. A. Analysis of Mediation Effect of FIGO Staging on Treatment Plans and Survival Status; B. Analysis of Mediation Effect of Histologic Grading on Treatment Plans and Survival Status; C. Analysis of Mediation Effect of Maximum Diameter of Recurrent Lesions on Treatment Plans and Survival Status; D. Analysis of Mediation Effect of Number of Recurrent Lesions on Treatment Plans and Survival Status; E. Analysis of Mediation Effect of Post-treatment CA125 Levels on Treatment Plans and Survival Status; F. Analysis of Mediation Effect of Post-treatment HE4 Levels on Treatment Plans and Survival Status. Note: CME, Causal Mediation Effect; ADE, Average Direct Effect; FIGO, FIGO Staging; CA125, Cancer Antigen 125; HE4, Human Epididymis Protein 4.

findings highlight the importance of considering individual patient characteristics when selecting treatment regimens, as these characteristics can significantly affect treatment outcomes even if they do not mediate survival directly.

Despite its contributions, this study has limitations. As a single-center retrospective analysis, the findings may lack generalizability, and potential selection and information biases could impact the results. Additionally, the follow-up period may be insufficient to capture long-term treatment effects and distant prognoses. Future research should include multicenter studies with larger sample sizes to increase data diversity and reliability. Prospective randomized controlled trials are also needed to minimize biases and improve the validity of findings. Extending the follow-up period will enable a more comprehensive assessment of long-term efficacy and prognosis. These efforts will further validate the use of

nedaplatin combined with paclitaxel liposomes or docetaxel in treating ROC.

Conclusion

In conclusion, both nedaplatin combined with paclitaxel liposomes or docetaxel demonstrate consistent efficacy in treating ROC, significantly reducing tumor markers and inflammatory factors without increasing adverse reactions. However, nedaplatin combined with docetaxel appears to have a more pronounced effect on improving PFS, supporting its use as a preferred regimen in specific clinical scenarios.

Disclosure of conflict of interest

None.

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