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Clinical evaluation of bevacizumab intravenous infusion–associated bleeding risk and vascular stress under a vascular-protective management pathway in recurrent ovarian cancer

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Abstract: **Background**: Bevacizumab (BEV) is pivotal for anti-angiogenic therapy in recurrent ovarian cancer (ROC), but its real-world bleeding risk profile and standardized management remain to be refined, demanding tailored pharmacovigilance data for clinical decision-making. **Objectives**: This single-center retrospective study characterized BEV-related bleeding events, explored the association between vascular protection management and coagulation-fibrinolysis/inflammation markers and provided bleeding risk prevention guidance. **Methods**: This single-center retrospective study was conducted in Nanjing, China, from October 2024 to September 2025, with follow-up completed by December 2025. Data were extracted from electronic medical records, laboratory information systems, pharmacy records, infusion records, and nursing documentation. Bleeding was graded per CTCAE v5.0; vascular protection metrics and dynamic changes of biochemical markers (Hb, PLT, FIB, D-dimer, and CRP) were collected and analyzed. **Results**: 22.5% had any-grade bleeding and 15.8% grade ≥2 bleeding, mostly mucocutaneous and clustered in early treatment. Compared to the non-bleeding group, the bleeding group exhibited higher concomitant drug use, a higher prevalence of hypertension, and lower vascular protection compliance (all $P < 0.05$). Additionally, this group experienced significant declines in Hb, PLT, and FIB, alongside elevated D-dimer and CRP levels (all $P < 0.05$). **Conclusion**: BEV-related bleeding has distinct features, associated with concomitant drugs, inadequate vascular protection and abnormal coagulation/inflammation markers. Integrating pharmacovigilance and multispecialty vascular protection strategies can effectively mitigate bleeding risk and reduce treatment disruptions.

Keywords: Bevacizumab; Bleeding; Nursing management; Pharmacovigilance; Recurrent ovarian cancer; Vascular protection management

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INTRODUCTION

Patients with recurrent ovarian cancer (ROC) remain at a high risk of relapse and progression after multiple lines of therapy. In clinical practice, anti-angiogenic regimens based on bevacizumab (BEV) are commonly used to delay disease progression (Li *et al.*, 2021). Previous randomized trials and real-world studies have confirmed the clinical benefits of BEV combined with chemotherapy in recurrent disease, while also indicating that its toxicity profile is characterized by vascular adverse events, including hypertension, proteinuria and bleeding (Sait Bakir *et al.*, 2021; Gilbert *et al.*, 2023). Pharmacologically, vascular endothelial growth factor (VEGF) signaling is involved not only in tumor neovascularization but also in normal endothelial homeostasis and vascular repair. Under VEGF inhibition, endothelial barrier function and microvascular stability may be perturbed, thereby increasing bleeding susceptibility in settings such as elevated inflammatory burden, mucosal injury, or concomitant use of anticoagulants/antiplatelet agents/non-steroidal anti-inflammatory drug (NSAIDs) (Majidi *et al.*, 2023). A cross-tumor meta-analysis suggests that anti-angiogenic monoclonal antibodies such as BEV are associated with increased risks of all-grade and high-grade bleeding, underscoring the need for risk identification and standardized management to reduce avoidable events (Baradacs *et al.*, 2024).

Current evidence often focuses on overall incidence or adverse-event profiles. Substantial heterogeneity exists across studies in bleeding grading, observation windows and control of concomitant medications, limiting the comparability of real-world evidence (Guan & Gao, 2022; Donovan *et al.*, 2022). More importantly, toxicities related to anti-angiogenic therapy should not be approached solely as a reactive "manage after the event" model; rather, they require a full-cycle "vascular-protective management" pathway. This pathway includes pre-infusion risk screening, monitoring of key indicators such as blood pressure and proteinuria, concomitant medication review and continuous patient education and follow-up (Sessa *et al.*, 2025). Practice-oriented recommendations emphasize assessing and controlling blood pressure before initiating

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BEV, continued monitoring of blood pressure and proteinuria during treatment, and treatment interruption or adjustment when necessary (Raychaudhuri *et al.*, 2025). In routine infusion settings, nursing teams conduct point-of-care assessments, monitor vital signs, observe for bleeding signs, provide patient education, and issue follow-up reminders—efforts that directly impact the timeliness of risk detection and escalation. When integrated with pharmacist-led prescription review and medication coordination, these steps form an auditable, actionable loop (Guler & Mete, 2023). Yet, quantitative evidence linking nursing process indicators to bleeding outcomes remains scarce.

Accordingly, this single-center retrospective cohort study evaluates the triad of vascular-protective management (including nursing monitoring and education), bleeding outcomes, and vascular-stress phenotypes. First, using the uniform Common Terminology Criteria for Adverse Events (CTCAE) grading system and a prespecified time window, this study describe the spectrum and timing of infusion-related bleeding. Second, it explores dynamic changes in routinely available coagulation–fibrinolysis, inflammatory and urinary protein measures to provide an accessible biochemical context for pharmacovigilance and multidisciplinary management.

MATERIALS AND METHODS

Sample size estimation

This single-center study was conducted at the General Hospital of the Eastern Theater Command, a tertiary-grade A general hospital located in Nanjing, Jiangsu Province, China. Patients were enrolled from October 2024 to September 2025, with < 90-day follow-up completed by December 2025. Sample size estimation followed a precision-based approach for a proportion. Sait Bakir et al. (2021) reported bleeding as an adverse-event count rather than as a CTCAE grade-specific 90-day bleeding incidence; bleeding occurred in 1 of 65 patients (1.5%) receiving chemotherapy plus bevacizumab and in 0 of 80 patients receiving chemotherapy alone. Therefore, this reference was used to confirm that bleeding was captured as a bevacizumab-related adverse event, whereas the expected incidence for the present pharmacovigilance-oriented sample size estimation was conservatively set at p=0.15. A 95% confidence interval half-width (d=0.07) was selected to ensure sufficient precision for clinical decision-making, consistent with the sample size design principles for pharmacovigilance studies in gynecologic oncology (Gaitskell *et al*., 2023). With $Z_{\alpha/2}$ = 1.96, the required sample size was approximately 100. Allowing for ~10% invalid or missing information, the target sample size was approximately 110, within the planned cap of 120.

Study population

Patients with ROC (including fallopian tube carcinoma and primary peritoneal carcinoma) who received BEV intravenous infusion at General Hospital of Eastern Theater Command between patients were enrolled from October 2024 to September 2025, with < 90-day follow-up completed by December 2025. Data were obtained from the electronic medical record (EMR), infusion records, laboratory information system (LIS), pharmacy medication records and nursing documentation. The follow-up window was defined from the first infusion to a maximum of 90 days, or until the primary endpoint (discontinuation of BEV), transfer, or death (whichever occurred first). This retrospective study was approved by the Institutional Review Board (IRB) of the General Hospital of Eastern Theater Command (No.2024DZKY-103-02). The IRB waived informed consent due to the study's retrospective nature and the use of de-identified clinical data, in accordance with the Declaration of Helsinki.

Follow-up

One hundred and twenty out of 137 potential study subjects were screened for study, and excluded patients included: active severe bleeding or uncontrolled hemorrhagic disease before infusion (n=4), combined severe hematological diseases (n=3), severe loss of key clinical variables (>30%, n=6) and concurrent participation in interventional trials altering bleeding risk (n=4). No patients were lost to follow-up during the 90-day follow-up period and all 120 enrolled patients completed the full follow-up with complete outcome data collection.

Inclusion and exclusion criteria

Inclusion criteria: Female ≥18 years old; definite diagnosis; ≥1 BEV infusion during the study period; traceable records of bleeding events and key baseline data; baseline laboratory tests (the most recent one within 7 days before infusion), including at least one of blood routine and coagulation-related items.

Exclusion criteria: Active severe bleeding or uncontrolled hemorrhagic disease before infusion; combined severe hematological diseases that cannot be adjusted; inability to determine the primary outcome or severe loss of key variables (e.g., >30%); concurrent participation in interventional trials that significantly alter bleeding risk and cannot be adjusted.

Information on herbal drugs, dietary supplements and other concomitant medications (excluding anticoagulants, antiplatelet agents, and NSAIDs) was collected from electronic medical records and pharmacy medication records for all enrolled patients.

Intervention and vascular-protective management pathway

Bevacizumab (Qilu Pharmaceutical Co., LTD, S20190040) was administered intravenously at a standard dose of 15 mg/kg every 3 weeks or 7.5 mg/kg every 2 weeks, in combination with platinum-based or non-platinum

chemotherapy regimens per clinical practice guidelines for recurrent ovarian cancer. No study-specific interventions were implemented. BEV doses/intervals and concurrent chemotherapy regimens were extracted from routine clinical records. Vascular-protective management was defined as traceable safety management elements for anti-VEGF therapy, delivered via a closed-loop process involving pharmacy and nursing teams:

Pharmacy management: Reconciliation of concurrent medications (e.g., anticoagulants, antiplatelet agents, NSAIDs) and prescription review alerts; documentation of adjustment recommendations or intensified monitoring when appropriate.
Nursing components: (1) Pre-infusion assessment: screening for bleeding symptoms (epistaxis/gingival bleeding/melena/hematuria/abnormal vaginal bleeding, etc.), inquiry about puncture/surgical history and menstrual status. (2) Monitoring during infusion: standardized measurement of blood pressure and pulse; observation for mucocutaneous bleeding signs and infusion-line conditions; avoidance of unnecessary invasive procedures and inadequate local compression. (3) Discharge and home education: emphasis on bleeding warning symptoms, avoidance of self-medication with NSAIDs, home blood pressure monitoring and reminders for laboratory follow-up. (4) Follow-up reminders: traceable records of telephone/clinic follow-up and feedback on abnormal results. Blood pressure and proteinuria monitoring followed existing guidelines (e.g., regular pre- and on-treatment measurements, quantitative proteinuria surveillance), with "timely completion of records" as a process indicator.

Laboratory measurements
All measurements were derived from routine clinical sampling without additional invasive procedures. Variables included hemoglobin (Hb), platelet count (PLT), prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (APTT), fibrinogen (FIB), D-dimer, C-reactive protein (CRP), liver and renal function indices and urinary protein (semi-quantitative, quantitative, or urine protein-to-creatinine ratio when available). Time windows were defined as baseline (within 7 days before infusion) and on-treatment (within 3 days before each infusion, if available).

Outcome measures
Primary outcomes: bleeding events within 90 days (any grade, grade ≥2, grade ≥3), anatomical distribution, time to first bleeding and management/actions including treatment adjustment (delay/hold/discontinuation) and supportive care. Bleeding was graded according to CTCAE v5.0 (Aktas *et al.*, 2025).

Secondary outcomes: dynamic changes in vascular-stress–related biomarkers (Hb, PLT, PT/INR, APTT, FIB, D-dimer, CRP, urinary protein); non-bleeding anti-VEGF adverse events (hypertension, proteinuria, thrombosis); and process indicators including attainment of blood pressure/urinary protein monitoring, pharmacy review and adjustment, nursing assessment documentation, education and follow-up documentation.

Statistical analysis
Continuous variables are presented as mean±SD or median interquartile range (IQR) and categorical variables as n (%). Between-group comparisons used the t test or Mann–Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Between group comparisons used the t test, within-group longitudinal changes from baseline to on-treatment were evaluated using the paired t-test. Multivariate logistic regression analysis was performed to identify independent predictors of grade ≥2 bleeding events, with variables including anticoagulant/antiplatelet/NSAIDs exposure, hypertension history and baseline coagulation markers (Hb, D-dimer, FIB) as covariates; odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for each independent predictor. A two-sided $P<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics and differences between bleeding and non-bleeding groups
All enrolled patients received BEV in the recurrent setting for platinum-resistant or platinum-sensitive recurrent ovarian cancer; no patients were treated with BEV in the first-line or maintenance setting. This homogeneous treatment setting eliminated confounding bias from different clinical application scenarios of BEV. Patients were stratified by CTCAE grade ≥2 bleeding: bleeding group (n=19) and non-bleeding group (n=101) (patients were stratified by the predefined threshold of CTCAE grade ⩾2 bleeding; the grade ⩾2 bleeding group included 19 patients, comprising 14 patients with grade 2 bleeding and 5 patients with grade ⩾3 bleeding. The remaining 101 patients were used as the comparator group and included patients without bleeding or with grade 1 bleeding). The bleeding group had a significantly higher rate of anticoagulant/antiplatelet or NSAID use ($P<0.001$). Notably, the prevalence of hypertension was significantly higher in the bleeding group than in the non-bleeding group ($P=0.025$), while there was no statistically significant difference in the proportion of patients with a history of gastrointestinal disease between the two groups ($P=0.103$). Baseline differences in Hb, PLT, D-dimer, PT/INR and FIB are presented in Table 1, suggesting bleeding outcomes associate with specific baseline traits related to "concurrent medication exposure—hemostatic capacity/fibrinolytic stress. Multivariate logistic regression analysis showed that anticoagulant/antiplatelet/NSAIDs exposure was an independent predictor of grade ≥2 bleeding events after adjusting for hypertension history and baseline coagulation markers (Hb, D-dimer, FIB) (OR=4.21, 95% CI: 1.57–11.28, $P=0.004$).

Table 1: Baseline characteristics of patients in the bleeding and non-bleeding groups

Indicators	Bleeding group (n=19)	Non-bleeding group (n=101)	Statistic (t or χ^2)	P Value
Age (years)	56.47±6.10	55.75±8.61	0.349	0.728
Anticoagulant/antiplatelet/NSAIDs exposure	12(63.2%)	25(24.8%)	11.063	<0.001
Hypertension history	10(52.6%)	27(26.7%)	5.030	0.025
Gastrointestinal disease history	7(36.8%)	20(19.8%)	2.663	0.103
Baseline Hb (g/L)	116.09±10.85	124.64±12.27	2.834	0.005
Baseline PLT (×10⁹/L)	207.01±80.05	235.50±66.56	1.656	0.100
Baseline D-dimer (mg/L)	1.85±0.63	1.27±0.59	3.936	<0.001
Baseline PT/INR	1.08±0.14	1.05±0.12	0.943	0.348
Baseline FIB (g/L)	3.17±0.81	3.81±1.05	4.986	<0.001

Table 2: Process indicators of vascular protection management between the bleeding and non-bleeding groups

Process indicators of management	Bleeding group (n=19)	Non-bleeding group (n=101)	Statistic (χ^2)	P value	Overall level (n=120)
Complete rate of pre-infusion blood pressure recording	15(78.9%)	95(94.1%)	4.781	0.029	110(91.7%)
Blood pressure compliance rate (control target <140/90mmHg)	12(63.2%)	86(85.1%)	5.165	0.023	98(81.7%)
Completion rate of urine protein/urine routine according to time window	14(73.7%)	92(91.1%)	4.701	0.030	106(88.3%)
Recording rate of pharmaceutical prescription review for high-risk combined medications	16(84.2%)	96(95.0%)	3.019	0.082	112(93.3%)
Recording rate of pre-infusion bleeding symptom screening	15(78.9%)	94(93.1%)	3.830	0.050	109(91.0%)
Recording rate of discharge/home education	13(68.4%)	88(87.1%)	4.200	0.040	101(84.2%)
Traceability rate of follow-up reminders/telephone follow-up	12(63.2%)	85(84.2%)	4.552	0.033	95(79.2%)

Table 3: Spectrum, grading, and temporal distribution of bleeding adverse events

Bleeding-related indicators	Value/Distribution characteristics
Incidence of any-grade bleeding	27 (22.5%)
CTCAE grade 1 bleeding	8/120 (6.7%); 8/27 (29.6% of any-grade bleeding)
CTCAE grade 2 bleeding	14/120 (11.7%); 14/27 (51.9% of any-grade bleeding)
CTCAE grade 3 bleeding	5/120 (4.2%); 5/27 (18.5% of any-grade bleeding)
Incidence of CTCAE grade ≥2 bleeding	19 (15.8%)
Incidence of CTCAE grade ≥3 bleeding	5 (4.2%)
Top 3 most common bleeding sites	1. Mucocutaneous (epistaxis/gingival bleeding): 13(48.1%); 2. Gastrointestinal tract (melena/hematochezia): 7 (25.9%); 3. Genitourinary tract (hematuria/abnormal vaginal bleeding): 7(25.9%)
Median time to first bleeding (IQR)	33 days (19~58 days)
Early aggregation characteristics of bleeding events	17 (63.0%) occurred within the first 4 treatment cycles
Proportion of treatment adjustment (delay/suspension/discontinuation)	10 (37.0%)
Proportion requiring blood transfusion/hemostatic treatment	8(29.63%)
Proportion of hospitalization due to bleeding	4(14.8%)
Proportion of active reporting of bleeding warning symptoms	14(51.9%)

Process indicators of vascular protection management and inter-group differences

The pre-infusion blood pressure recording rate was 91.7%, 78.9% in the bleeding group and 94.1% in the non-bleeding group (P=0.029); the blood pressure compliance rate was 63.2% and 85.1%, respectively (P=0.023). The completion rate of urine protein/urine routine according to the time window was 73.7% and 91.1% respectively (P=0.030). The

recording rate of pharmaceutical prescription review for high-risk combined medications was 93.3%, and the difference between the two groups was that the bleeding group (84.2%) was lower than the non-bleeding group (95.0%) (P=0.082). Regarding nursing-related process indicators, the recording rate of pre-infusion bleeding symptom screening was 91.0% (78.9% in the bleeding group vs 93.1% in the non-bleeding group, P=0.050); the recording rate of discharge/home education was 84.2% (P=0.040); the traceability rate of follow-up reminders/telephone follow-up was 79.2% (P=0.033). Overall, the management differences were mainly concentrated in operable links such as monitoring compliance and education follow-up (Table 2).

Spectrum, grading and temporal distribution of bleeding adverse events

Within 90 days of follow-up, 22.5% of patients experienced any-grade bleeding, 15.8% grade ≥2 bleeding and 4.2% grade ≥3 bleeding. Mucocutaneous bleeding (epistaxis/gingival bleeding) was most common, followed by gastrointestinal (melena/hematochezia) and genitourinary (hematuria/abnormal vaginal bleeding) bleeding. The median time to first bleeding was 33 days (IQR 19–58), with events clustering in the early treatment phase. Regarding management and outcomes: 37.0% of patients required a treatment adjustment (delay/hold/discontinuation), 25.9% needed blood transfusion/hemostatic therapy, and 14.8% were hospitalized for bleeding; nursing records indicated that 51.9% of patients actively reported bleeding warning symptoms (Table 3).

Clinical characteristics and treatment outcomes of bleeding events

The bleeding grade distribution was CTCAE grade 2 (n=14) and grade 3 (n=5). The spectrum of bleeding types and sites, time from the first infusion, the proportion more common after the 1-4th infusion, as well as treatment methods (symptomatic/hemostatic, blood transfusion, interventional/endoscopic/surgical) and subsequent BEV treatment (continuation/delay/discontinuation) are detailed in table 4.

Dynamic changes of vascular stress-related biochemical indicators

All on-treatment biomarker measurements (Hb, PLT, FIB, D-dimer, CRP) were collected 1–3 days before the occurrence of bleeding events (for the bleeding group) or at the corresponding treatment time points (for the non-bleeding group). In the non-bleeding group, baseline and on-treatment Hb, PLT, and FIB levels showed no significant differences (P > 0.05). However, D-dimer and CRP levels significantly increased during treatment (P < 0.05). Between-group comparisons revealed that the bleeding group had lower on-treatment Hb, PLT, and FIB, and higher CRP (P<0.05). Similarly, baseline-to-treatment changes were more pronounced in the bleeding group than in the non-bleeding group (P<0.05) (Fig. 1). These findings confirmed the presence of BEV-induced endothelial dysfunction, which is the core cause of the simultaneous decrease in Hb, PLT and FIB.

Spectrum and management response of non-bleeding anti-VEGF-related adverse events

The incidence of hypertension was 31.7% (grade ⩾2, 13.3%), proteinuria was 20.8% (grade ⩾2, 7.5%), and thrombotic events were 4.2%. Corresponding management responses: 76.3% of patients initiated/adjusted antihypertensive treatment, 100% received enhanced urine protein follow-up and 80.0% had adjusted antithrombotic strategies (Table 5). The significantly higher incidence of hypertension and proteinuria in the bleeding group suggested that vascular endothelial damage induced by anti-VEGF therapy is a common pathological basis for multiple vascular adverse events and uncontrolled hypertension and persistent proteinuria may further increase the risk of bleeding by aggravating vascular fragility and microcirculation dysfunction.

DISCUSSION

In this single-center cohort with 90-day follow-up, bleeding during BEV infusion exhibited distinct grade and site spectra, with a tendency to cluster early after treatment initiation. Patients with clinically meaningful bleeding differed from those without bleeding in specific baseline exposures, adherence to vascular-protective management processes (including nursing documentation) and trajectories of coagulation-fibrinolysis/inflammation-related biomarkers.

Randomized evidence has established the clinical role of BEV in ROC (Gallego *et al.*, 2021). In OCEANS (platinum-sensitive recurrence) and AURELIA (platinum-resistant recurrence), vascular toxicities, such as hypertension, proteinuria, and bleeding, were repeatedly observed, reinforcing the need for pharmacovigilance when balancing benefit against risk (Sait Bakir *et al*., 2021; Gilbert *et al*., 2023). Both reported toxicity spectra consistent with anti-VEGF mechanisms mechanisms, including hypertension, proteinuria and bleeding, suggesting that continuous pharmacovigilance is required when benefits and risks coexist. From broader evidence, meta-analyses indicate that BEV plus chemotherapy is associated with increased high-grade bleeding risk and that the risk may vary with dose and tumor type. Overall, anti-angiogenic monoclonal antibodies are associated with increased all-grade and high-grade bleeding risk, supporting the need for process-based risk control in real-world settings (Wu *et al.*, 2024; Akilli *et al.*, 2022). Therefore, presenting bleeding events alongside management process indicators aligns with the translational goal of pharmacovigilance research.

Table 4: Clinical characteristics and treatment outcomes of bleeding events

Bleeding grade	Number of cases (n)	Main bleeding sites	Median time from first infusion (days)	Treatment methods	Subsequent BEV treatment
CTCAE Grade 2	14	Mucocutaneous (9), Genitourinary tract (5)	29 (17~47)	Symptomatic treatment [local hemostasis/observation] [10], Hemostatic drugs [4]	Continued treatment [9], Delay for 1~2 weeks [5]
CTCAE Grade 3	5	Gastrointestinal tract (3), Genitourinary tract (2)	45 (28~65)	Hemostatic drugs [1], Blood transfusion [3], Endoscopic intervention [1]	Suspended treatment [3], Permanent discontinuation [2]
CTCAE Grade 4	0	-	-	-	-
Total (Grade ≥2)	19	-	33 (19~58)	-	-

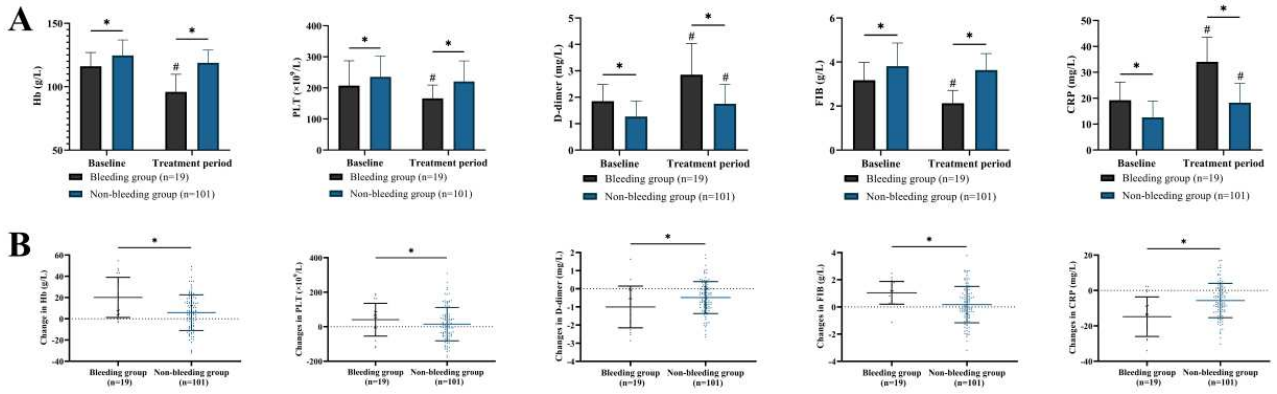

Fig. 1: Dynamic changes of vascular stress-related biochemical indicators (Hb, PLT, FIB, D-dimer, and CRP) between the bleeding and non-bleeding groups. The non-bleeding group was defined as CTCAE grade <2 bleeding, whereas the bleeding group was defined as CTCAE grade ≥2 bleeding.
(A) This panel shows biomarker levels at baseline and during the treatment period; (B) This panel shows baseline-to-treatment changes (Δ values) in each biomarker between the two groups. Data are presented as mean ± SD, and error bars indicate SD. *P<0.05 indicates a significant between-group difference at the same time point in panel A or a significant between-group difference in Δ values in panel B; #P<0.05 indicates a significant within-group change compared with baseline. Between-group comparisons were performed using the independent-samples t test, and within-group baseline-to-treatment comparisons were performed using the paired t test.

Table 5: Spectrum of non-bleeding anti-VEGF-related adverse events and corresponding management responses

Types of adverse events	Incidence (n=120)	Incidence of grade ≥2	Management response measures and proportions
Hypertension	38(31.7%)	16(13.3%)	Initiation/adjustment of antihypertensive treatment: 29(76.3%)
Proteinuria	25(20.8%)	9(7.5%)	Enhanced urine protein follow-up: 25(100%), Suspended treatment: 5(20.0%)
Thrombosis events	5(4.2%)	5(4.2%)	Adjustment of antithrombotic strategy: 4(80.0%), Discontinuation of BEV: 1(20.0%)
Others (fatigue/gastrointestinal reactions)	21(17.5%)	4(3.3%)	Symptomatic treatment: 21(100%)

This study confirmed that the standard dose of 15 mg/kg q3w or 7.5 mg/kg q2w is associated with a manageable high-grade bleeding risk (4.2%), which is in line with the meta-analysis by Gaitskell *et al*. that concluded moderate-dose bevacizumab has a favorable risk-benefit ratio in recurrent ovarian cancer (Gaitskell *et al.*, 2023). Overall,

anti-angiogenic monoclonal antibodies are associated with increased all-grade and high-grade bleeding risk, supporting the need for process-based risk control in real-world settings. This temporal association directly supports the conclusion that acute endothelial destabilization is the immediate cause of BEV-related early bleeding events. Therefore, presenting bleeding events alongside management process indicators aligns with the translational goal of pharmacovigilance research.

The synergistic effect of pre-existing coagulation-fibrinolytic dysregulation (elevated D-dimer + reduced FIB) and BEV-induced endothelial dysfunction is the key biological mechanism for increased bleeding risk. Mechanistically, VEGF inhibition can compromise endothelial function and microvascular homeostasis, thereby reducing the capacity of the vascular barrier to maintain integrity and repair. The study of supports this pathological mechanism (Zak *et al.*, 2024), which found that VEGF inhibition downregulates endothelial cadherin expression, leading to increased vascular permeability and fragility and this study's finding of lower FIB and higher D-dimer in the bleeding group further verifies this mechanism from the perspective of coagulation-fibrinolysis dysregulation. The "coagulation–fibrinolysis and inflammatory stress phenotype" observed in the bleeding group (e.g., differences and dynamic changes in D-dimer, FIB and CRP) is biologically plausible. This finding is consistent with the study of Dong *et al*., which found that D-dimer elevation and FIB reduction are independent risk factors for bleeding events in patients receiving anti-angiogenic therapy (Dong *et al.*, 2021). Wakasa *et al*. (2024) also reported that baseline CRP ≥10 mg/L is a predictor of bevacizumab-related vascular adverse events in ovarian cancer patients (Wakasa *et al.*, 2024), which is consistent with this study's results and supports the use of CRP as a routine monitoring indicator. This confirms that the observed CRP elevation in this study reflects BEV-induced vascular endothelial injury and subsequent local vascular inflammation, rather than systemic inflammation caused by tumor burden. Importantly, these indicators are routinely available in clinical practice, making them feasible for incorporation into monitoring pathways jointly implemented by pharmacists and nurses.

A further point is that this study operationalized "vascular-protective management" into auditable process indicators and explicitly incorporated nursing components. Practice-oriented recommendations emphasize the evaluation and control of blood pressure before BEV initiation, continued monitoring of blood pressure during therapy, and quantification and follow-up of proteinuria; when blood pressure remains uncontrolled or proteinuria worsens, treatment delay or interruption, and targeted management should be considered (Khanmammadov *et al.*, 2024). Nursing teams, through day-of-infusion vital-sign monitoring, observation for bleeding signs, symptom inquiry, patient education and follow-up reminders, can serve as a frontline mechanism for "early detection–timely feedback–coordinated response" (Inci *et al.*, 2023). Pharmacists provide systematic prescription review and recommendations regarding concomitant medication risks and potential interactions. When nursing documentation and pharmacist review form a closed-loop feedback process, risk can be shifted upstream to the period before events occur, rather than to the period after bleeding develops. In this cohort, differences in monitoring attainment and education/follow-up traceability between groups suggest that strengthening these processes may be feasible. Nonetheless, retrospective associations should not be over-interpreted as causal, particularly given potential confounding from chemotherapy-related myelosuppression, tumor burden, and differences in comorbidity; multivariable adjustment and sensitivity analyses are therefore essential for cautious interpretation.

Based on these findings, ntegration of nursing assessment and pharmacy prescription review into standardized vascular protection management: complete bleeding symptom screening and home blood pressure monitoring education prior to BEV initiation; intensify blood pressure and urine protein follow-up reminders during the first 2 treatment cycles; implement "double verification" (pharmacist prescription review + nurse education) for patients on concurrent anticoagulants/antiplatelets/NSAIDs; and shorten follow-up intervals for timely assessment if warning symptoms (e.g., epistaxis, melena, hematuria) or abnormal Hb/PLT levels emerge.

Limitations of this study include: first, the single-center, retrospective design may introduce selection and information bias, and it is difficult to quantify the quality of nursing education and patient compliance accurately; second, the sample size and number of events are limited. Although multivariate analysis is used, residual confounding may still exist and differences in myelosuppression caused by different combined chemotherapy regimens may affect bleeding outcomes; third, the maximum follow-up period is 90 days, which only reflects short-term infusion period risks and cannot infer the event spectrum in the long-term maintenance phase; fourth, some laboratory indicators are missing during the event window, which may affect the robustness of dynamic comparison; fifth, mild bleeding may be treated by patients themselves in external hospitals or outpatient clinics without complete records. The above factors all suggest that subsequent multi-center studies with longer follow-up are needed to verify external validity.

CONCLUSION

BEV infusion-period bleeding in ROC exhibits recognizable clinical patterns, with associations to coagulation-fibrinolysis/inflammatory stress phenotypes and vascular-protective management process indicators (including nursing monitoring and education/follow-up). Embedding pharmacovigilance, pharmacy management and nursing management throughout the treatment course—with intensified early monitoring—may reduce clinically meaningful bleeding and support treatment continuity.

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Author contribution statement
Aomei Li and Jixian Zang conceived and designed the project, Tingting Li wrote the paper. Lili Wan generated the data, Xin Wang and Dongyun Wu analyzed the data, Aomei Li and Jixian Zang modified the manuscript. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval
The study was approved by the ethics Committee of the General Hospital of Eastern Theater Command (2024DZKY-103-02). This study was performed in adherence with the RECORD guidelines. See supplementary file for the RECORD checklist.

Conflict of interest
The authors report no conflict of interest.

Supplementary data
https://www.pjps.pk/uploads/2026/07/SUP1784551206.pdf

REFERENCES

Akilli H, Rahatli S, Aliyeva K, Altundag O, Kuscu UE and Ayhan A (2022). Survival in recurrent ovarian cancer patients before and after the bevacizumab era: An observational single-centre study. *J Obstet Gynaecol*, **42**(6): 2230-2234.

Aktas A, Kadakia KC, Waldman J and Walsh D (2025). Weight loss in cancer and the 2017 common terminology criteria for adverse events-dangerous and misleading. *J Cachexia Sarcopenia Muscle*, **16**(2): e13754.

Baradacs I, Teutsch B, Varadi A, Bila A, Vincze A, Hegyi P, Fazekas T, Komoroczy B, Nyirady P, Acs N, Banhidy F and Lintner B (2024). PARP inhibitor era in ovarian cancer treatment: a systematic review and meta-analysis of randomized controlled trials. *J Ovarian Res*, **17**(1): 53.

Dong X, Liu X, Liu Y, Jiang L, Zhang H and Liu B (2021). Clinical efficacy of conventional heparin anticoagulation combined with apixaban in the treatment of patients with cerebral venous thrombosis and its effect on serum D-dimer and FIB expression. *Comput Math Methods Med*, **2021**: 4979210.

Donovan HS, Sereika SM, Wenzel LB, Edwards RP, Knapp JE, Hughes SH, Roberge MC, Thomas TH, Klein SJ, Spring MB, Nolte S, Landrum LM, Casey AC, Mutch DG, DeBernardo RL, Muller CY, Sullivan SA and Ward SE (2022). Effects of the WRITE symptoms interventions on symptoms and quality of life among patients with recurrent ovarian cancers: An NRG oncology/GOG study (GOG-0259). *J Clin Oncol*, **40**(13): 1464-1473.

Gaitskell K, Rogozinska E, Platt S, Chen Y, Abd El Aziz M, Tattersall A and Morrison J (2023). Angiogenesis inhibitors for the treatment of epithelial ovarian cancer. *Cochrane Database Syst Rev*, **4**(4): CD007930.

Gallego A, Ramon-Patino J, Brenes J, Mendiola M, Berjon A, Casado G, Castelo B, Espinosa E, Hernandez A, Hardisson D, Feliu J and Redondo A (2021). Bevacizumab in recurrent ovarian cancer: Could it be particularly effective in patients with clear cell carcinoma? *Clin Transl Oncol*, **23**(3): 536-542.

Gilbert L, Oaknin A, Matulonis UA, Mantia-Smaldone GM, Lim PC, Castro CM, Provencher D, Memarzadeh S, Method M, Wang J, Moore KN and O'Malley DM (2023). Safety and efficacy of mirvetuximab soravtansine, a folate receptor alpha (FRalpha)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer. *Gynecologic oncology*, **170**: 241-247.

Guan W and Gao H (2022). Potential of curcumin loaded nanoparticles in ovarian cancer: Investigation using gynecological color Doppler ultrasound technique. *Pak J Pharm Sci*, **35**(5): 1467-1471.

Guler B and Mete S (2023). Effects of relaxation-focused nursing program in women with ovarian cancer: A randomized controlled trial. *Pain Manag Nurs*, **24**(4): e35-e45.

Inci MG, Sehouli J, Schnura E, Lee M, Roll S, Reinhold T, Klews J, Kaufner L, Niggemann P, Groeben H, Toelkes J, Reisshauer A, Liebl M, Daehnert E, Zimmermann M, Knappe-Drzikova B, Rolker S, Nunier B, Algharably E, Pirmorady Sehouli A, Zwantleitner L, Krull A, Heitz F, Ataseven B, Chekerov R, Harter P and Schneider S (2023). The KORE-INNOVATION trial, a prospective controlled multi-site clinical study to implement and assess the effects of an innovative peri-operative care pathway for patients with ovarian cancer: Rationale,

methods and trial design. *Int J Gynecol Cancer*, **33**(8): 1304-1309.

Khanmammadov NJ, Dogan I, Okay NS, Azizy A, Saip P and Aydiner A (2024). Comparative analysis of doublet chemotherapy regimens plus bevacizumab in patients with recurrent ovarian cancer. *Medicine (Baltimore)*, **103**(1): e36750.

Li YT, Liu CH and Wang PH (2021). Treatment for recurrent epithelial ovarian cancer. *Taiwan J Obstet Gynecol*, **60**(5): 803-804.

Majidi A, Na R, Jordan SJ, DeFazio A, Obermair A, Friedlander M, Grant P and Webb PM (2023). Common analgesics and ovarian cancer survival: The ovarian cancer prognosis and lifestyle (OPAL) study. *J Natl Cancer Inst*, **115**(5): 570-577.

Raychaudhuri S, McLaughlin E, Pennell ML, Stefanick M, Reding K, Vasbinder A, Cheng RK, Barac A and Simon MS (2025). The relationship between cardiometabolic abnormalities and mortality in the Women's Health Initiative: A comparison of associations among women with cancer to women without cancer. *Cancer*, **131**(6): e35804.

Sait Bakir M, Birge O, Karadag C, Ilhan Y, Aykut Tuncer H, Sezgin Goksu S and Simsek T (2021). Bevacizumab in recurrent ovarian cancer. *J BUON*, **26**(4): 1271-1278.

Sessa C, Travado L, Calaminus G, Cunha TM, Delgado Bolton RC, van Driel W, Fernandes A, Hutka M, Lemley B, Luczak N, Medeiros R, Oberst S, Ottevanger N, Papadia A, Pereira P, Rodrigues M, Stolnicu S, Vandecasteele K, Costa A, Poortmans P and Peccatori F (2025). European cancer organisation essential requirements for quality cancer care for ovarian cancer: Focus on the multidisciplinary team. *Tumori*, **111**(1): 11-19.

Wakasa J, Iwakiri K, Ohta Y, Minoda Y, Kobayashi A and Nakamura H (2024). Perioperative bleeding control in total hip arthroplasty: Hemostatic powder vs. tranexamic acid-a prospective randomized controlled trial. *Arch Orthop Trauma Surg*, **144**(8): 3797-3805.

Wu D, He J, Shi P, Wang Z, Liu M and Liu A (2024). Quality of life in ovarian cancer patients treated with bevacizumab: A meta-analysis. *Expert Opin Drug Saf*, **23**(3): 269-276.

Zak K, Satora M, Skrabalak I, Tarkowski R, Ostrowska-Lesko M and Bobinski M (2024). The potential influence of residual or recurrent disease on bevacizumab treatment efficacy in ovarian cancer: Current evidence and future perspectives. *Cancers (Basel)*, **16**(5): 1063.