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Original Research

Comparison of pharmacovigilance and mechanism analysis of the vascular toxicity caused by platin-based chemotherapy: integration of FAERS analysis, network pharmacology, and endothelial validation

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Abstract

Background: Understanding of the possible vasoactive toxicities associated with platinum-containing chemotherapeutic drugs for solid tumors remains limited.

Objectives: This study comprehensively identifies the vessel-threatening effects of cisplatin (CDDP), carboplatin (CBP), and oxaliplatin (OXA) and aims to compile an analytical model.

Design: A retrospective pharmacovigilance study was combined with network pharmacology analysis and in vitro experimental validation.

Methods: Disproportionality analyses, including reporting odds ratio, proportional reporting ratio, empirical Bayesian geometric mean, and Bayesian confidence propagation neural network, were conducted to identify vascular adverse events (VAEs) related to the three drugs using data from the FDA Adverse Event Reporting System (FAERS) database from 2004 to 2024. Network pharmacology was used to identify potential molecular targets and pathways. Human umbilical vein endothelial cells were treated with cisplatin, carboplatin, or oxaliplatin to evaluate cell viability (CCK-8 assay), apoptosis (flow cytometry), and gene expression by reverse transcription quantitative polymerase chain reaction (RT-qPCR) including Nrf2, ICAM1, VCAM1, NOS3, and HIF1A.

Results: Among the 10,536 VAEs identified, all three drugs showed strong correlations with vascular events. Oxaliplatin had a correlation coefficient of 2.05 (95% confidence interval (CI): 1.99–2.11). Early failure characteristics (Weibull $\beta \leqslant 1$) were observed for all three drugs. The most frequently reported VAEs were hypotension, flushing, hypertension, and thrombosis. Network analysis highlighted the HIF-1, EGFR, and oxidative stress pathways. In vitro, oxaliplatin significantly reduced Nrf2 expression and cell viability, while cisplatin upregulated ICAM1 expression.

Conclusion: Platinum compounds induce a short-term vasoconstrictive effect, with oxaliplatin showing a relatively lower association. The results suggest activation of the oxidative stress pathway through Nrf2 inhibition and increased ICAM1 levels, alongside pathway-specific alterations such as reduced HIF1A and NOS3 expression and decreased VCAM1 levels. Early cardiovascular monitoring and Nrf2-targeted therapy warrant further investigation.

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Plain language summary

Are the risk of blood vessel damage by platinum-based chemotherapy drugs different? Evidence from real-world safety data and laboratory tests

Many types of platinum-containing chemotherapy agents that can be applied in various kinds of cancer treatment. Although the anti-cancer effect is clear; The impact of them on Blood Vessels has been insufficiently studied. vascular Side Effects can lead to Problems such as fluctuations in blood pressure, thromboembolism or other clotting Disorders and dysfunction of vessel lumen. Combining large-scale real-world drug-safety Data with Laboratory experiments in combination for comparison of vascular Risks among Platinum Drugs and identification or exploration of potential Biological Mechanisms. Based on analysis of the world's safety reports, all three agents had a high incidence rate of vascular complications soon after administration. oxaliplatin was most strongly associated with vascular events; carboplatin had the lowest risk. Laboratory experiment Results: Platinum compounds decrease the number of human endothelial cells and promote their death. Oxaliplatin inhibited the activity of a key antioxidant protection pathway; cisplatin up-regulated the expression of inflammatory adhesion molecules and caused similar endothelial dysfunction effects as oxaliplatin. Based on the above result, it has been found that increasing one's age will trigger early vascular damage caused by platinum drugs; Moreover, different chemotherapy treatment methods have varying effectiveness outcomes.

Keywords: endothelial dysfunction, HIF-1 pathway, Nrf2 signaling, platinum-based chemotherapy, vascular adverse events

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Introduction

Endothelial cells constitute the largest proportion of cells within the vessel wall, where they maintain biological barriers and support vascular homeostasis. They participate in regulating fundamental physiological activities such as vasodilation, vasoconstriction, barrier permeability regulation, the balance between coagulation and fibrinolysis, and immune-inflammatory responses.[1,2] Under healthy conditions, endothelial cells reside in an anti-inflammatory, antithrombotic, and vascular compliant state, which is associated with the secretion of vasodilatory factors such as nitric oxide (NO) and the silencing of adhesion molecules. Nevertheless, specific conditions such as oxidative stress, inflammatory stimuli, and metabolic defects can alter endothelial function. This altered state is characterized by decreased NO production, increased expression of adhesion molecules, and impaired vascular responses, ultimately leading to vascular stiffening, thrombosis, and microcirculatory dysfunction.[3] Endothelial dysfunction has been considered an early event in the development of vascular pathology and a contributor to its progression.[4]

Platinum-containing chemotherapeutic agents, including cisplatin (CDDP), carboplatin (CBP), and oxaliplatin (OXA), are classified as first-line standard drugs for treating various solid tumors, such as lung cancer, ovarian cancer, gastric cancer, and head and neck squamous cell carcinoma.[5] Although platinum drugs exhibit certain anti-tumor effects, the extended survival of patients undergoing these treatments has been associated with a significantly increased risk of cardiovascular disease. Clinical evidence indicates that patients treated with cisplatin regimens experience severe vascular stiffening, metabolic disorders, and early atherosclerosis years after

treatment.[6] According to long-term follow-up data, a group of young patients who received cisplatin therapy demonstrated an excessively high risk of cardiovascular disease 20 years later.[7] Furthermore, acute vascular adverse events (VAEs), including hypertension, vasospasm, venous thrombosis, and arterial occlusive disease, can occur during platinum-based treatment.[8,9]

Mechanistic studies have shown that platinum-based drugs can cause endothelial damage in blood vessels and enhance inflammation by accelerating reactive oxygen species production, impairing mitochondrial function, reducing antioxidant activity, and increasing levels of inflammatory adhesion molecules.[10,11] Cisplatin blocks endothelial nitric oxide synthase (eNOS) and thereby inhibits NO production, leading to vasoconstriction and microcirculatory dysfunction. Oxaliplatin, on the other hand, is thought to potentially modulate blood flow responsiveness and vascular tone through autonomic reflex controls.[12] Nonetheless, limited systematic studies have compared the intensity and mechanisms of vascular toxicity among different platinum-based drugs, and it remains unclear whether this vascular damage follows a specific temporal pattern, such as early versus cumulative injury.

Real-world drug adverse event (AE) databases, such as FDA Adverse Event Reporting System (FAERS), reflect the characteristics of drug adverse reactions across the entire population and treatment cycle, helping to identify safety risks that may be inadequately assessed in clinical trials. Concurrently, network pharmacology analysis can elucidate drug-related gene targets and signaling pathways at the systems biology level, including inflammatory pathways, oxidative stress responses, and HIF-1 pathways. These signaling pathways have been suggested to be closely associated with endothelial injury.[12,13] Further integration with in vitro endothelial cell experiments is intended to validate these biological effects, thereby establishing a scientific closed-loop process that connects real-world signals with molecular mechanism inference and cellular phenotype validation.

Based on this framework, the present study systematically evaluated the association strength, event spectrum, and temporal characteristics of cisplatin, carboplatin, and oxaliplatin with VAEs using the FAERS database. This analysis was combined with network pharmacology to identify core signaling pathways and potential target genes related to vascular injury for carboplatin and oxaliplatin. The effects of each drug on cell viability, apoptosis, and inflammatory phenotype were also confirmed in vitro using human umbilical vein endothelial cells (HUVECs). This study aimed to establish theoretical foundations and clinical guidance for identifying vascular risks and implementing differentiated management strategies in platinum-based treatment.

Methods

Data source

Reporting of this pharmacovigilance study complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[14] FAERS, the US Food and Drug Administration's pharmacovigilance data platform, is deployed worldwide to collect adverse drug reactions from clinicians and patients and is currently maintained by the FDA.[12] The dataset consists of seven related files connected by unique identifiers to facilitate clean data extraction. We used all reports from the first quarter of 2004 to the fourth quarter of 2024, totaling 25,000,088 reports. We applied a two-step de-duplication procedure based on case identifiers and report versions,[15] which resulted in 18,640,061 reports in total. The de-duplication procedure is shown in Figure 1.

Case definition

VAEs were identified using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) of "Vascular Disorders" (MedDRA code: 10047065). The SOC-level definition was used to provide a broad and comprehensive initial evaluation of the potential vascular safety signal for platinum-based chemotherapy agents. Although this pathway involved multiple types of vessel diseases with varying disease mechanisms (such as thrombosis, hemodynamic disorders, and inflammation), it was chosen due to the exploratory nature of this pharmacovigilance study and because it has become an established practice for generating signals from spontaneous adverse reaction databases.[16,17] Future research should use finer-grained events for classification (clustering of similar terms through latent analysis) to improve signal

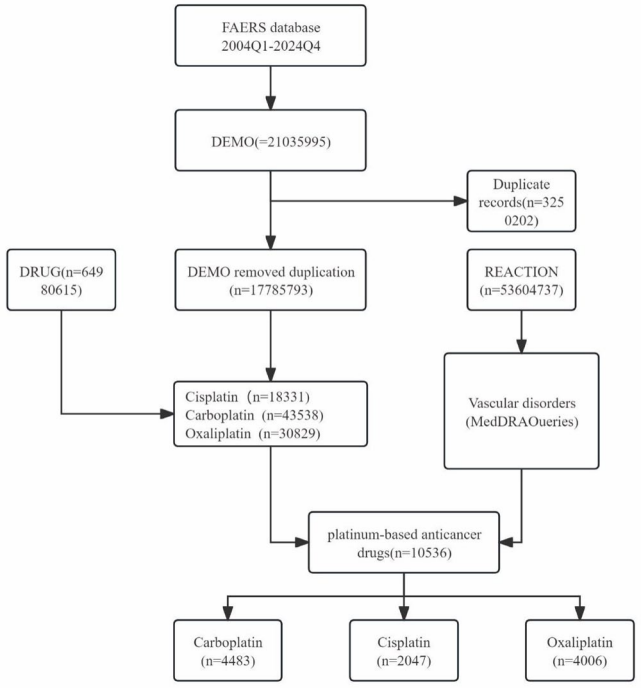

Figure 1. Flowchart of platinum-based drug selection and vascular AE identification from the FAERS database.
AE, adverse event; FAERS, FDA Adverse Event Reporting System.

refinement and provide more detailed mechanistic insights.

Data extraction

A retrospective pharmacovigilance study using disproportionality analysis was conducted to evaluate VAEs associated with platinum-based chemotherapy agents. The following search terms were used to identify relevant reports in the FAERS database: generic and brand names of cisplatin ("cisplatin," "Platinol"), carboplatin ("carboplatin," "Paraplatin"), and oxaliplatin ("oxaliplatin," "Eloxatin"). AEs were classified using the MedDRA version 26.1 and restricted to the SOC of "Vascular Disorders" (MedDRA code: 10047065).

Both generic and non-generic forms of platinum-containing chemotherapy drugs (cisplatin, carboplatin, and oxaliplatin) were used to identify adverse reactions in the FAERS drug file. Reports classified under the Vascular Disorders SOC (MedDRA code: 10047065) were selected for analysis.

Time-to-onset was determined by subtracting the period between the commencement of the drug (from the THER file) and the development of an AE (from the DEMO file). Only cases with a valid and positive time interval were included.[18] Reporting dates were excluded if they were unrecorded, inconsistent, or if drug administration occurred after the event onset.

Inclusion and exclusion criteria

The inclusion criteria for this study were as follows. First, reports had to contain any of the three platinum-based drugs of interest (cisplatin, carboplatin, or oxaliplatin) as the primary suspected drug. Second, AEs had to be classified under the SOC of "Vascular Disorders" (MedDRA code: 10047065). Third, reports had to include complete and valid information on drug administration dates and event onset dates for time to onset (TTO) analysis.

The exclusion criteria were as follows. Duplicate reports identified by de-duplication procedures based on CASEID and PRIMARYID were excluded. Reports in which the platinum-containing drugs were listed as co-medication factors rather than primary suspects were also excluded. Additionally, reports with missing or inconsistent data on essential indicators such as age, gender, or

medical record dates for entry into medical institutions or events were excluded. Finally, reports with an AE onset time earlier than the start of platinum-containing medication were excluded.

Signal mining and statistical analysis

Four types of disproportionality analysis methods were applied: Reporting Odds Ratios (ROR), Proportional Reporting Ratios, empirical Bayesian geometric means, and Bayes' confidence propagation neural networks. These were used to identify safety indicators for vascular complications. A signal was considered significant when the lower bound of the 95% confidence interval (CI) for ROR exceeded 1.[19] The calculation formulas and thresholds for these methods are presented in Table S1.

For sensitivity analysis, multivariable logistic regression was used to recalculate the association between platinum-containing drug use and vascular-related adverse effects, aiming to minimize potential sources of bias. Adjustments were made for confounding variables, and adjusted reporting odds ratios with 95% CIs were calculated. To ensure the validity of the multivariate analysis, reports with missing data on key covariates were excluded, and confounding factors that could potentially contribute to VAEs, along with other relevant clinical variables, were included in the logistic regression model. Subgroup analyses were conducted to further demonstrate the consistency of the results.

TTO was defined as the time interval between the start of platinum-based treatment (recorded in the THER file) and the occurrence of a vascular-related AE (recorded in the DEMO file). Goodness-of-fit analysis was performed using Weibull, gamma, and exponential distributions to determine the most suitable probabilistic model for TTO analysis. Two parameters, scale (α) and shape (β), characterized each distribution.

Logistic regression analysis was used to examine risk factors, including age, sex, and body weight, while excluding incomplete records. Statistical analyses were performed using R software (version 4.4.1, The R Foundation for Statistical Computing, Vienna, Austria).

Network pharmacology analysis

Screening active components and target prediction. Canonical SMILES representations of cisplatin, carboplatin, and oxaliplatin were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). These SMILES strings were then entered into the Target Prediction platform (https://prediction.charite.de/subpages/target_prediction.php) to predict potential protein target candidates. The resulting UniProt IDs were subsequently converted to corresponding gene names using the UniProt database.

Acquisition of lung cancer-associated genes. To construct a disease context for the network pharmacology analysis, we selected lung cancer as a representative disease model. This decision was based on the following considerations. First, lung cancer is one of the most common indications for platinum-based chemotherapy worldwide. Second, our research group has a longstanding focus on thoracic oncology, which made lung cancer a relevant and practical choice for this exploratory analysis. Third, the availability of well-curated, comprehensive gene datasets for lung cancer in public databases (OMIM and GeneCards) facilitated a robust initial exploration of potential drug-disease interactions. Platinum drugs are applied to various malignancies, including ovarian, digestive tract, and head and neck cancers, whereas vascular toxicity is not limited by the disease type. Therefore, this approach was intended as a proof-of-concept to identify potential toxicity-related pathways within a defined biological context, rather than to imply that the observed mechanisms are exclusive to lung cancer. Future research can explore cancers of various types to create a comprehensive assessment.

The OMIM and GeneCards databases were searched with the keyword "lung cancer," and gene targets related to lung cancer were obtained. The final gene list related to the disease was derived through integration and cleaning of the obtained results in Excel, which eliminated duplicates and unified identifiers.

Target overlap and visualization. To determine the overlap between therapeutic targets and lung cancer genes, an online tool named EVenn (https://bioinfogp.cnb.csic.es/tools/venny/) was used.[13] The overlapping targets were considered the potential therapeutic or toxicity-related genes.

Drug–ingredient–target network construction. The interaction framework among drugs, ingredients, and targets was constructed by importing

the platinum pharmaceuticals, active components, and intersecting targets into Cytoscape (version 3.9.1; The Cytoscape Project, https://cytoscape.org/). Nodes represented substances, components, or gene targets. Node connectivity was assessed based on the number of connections each node had.

Analysis of protein–protein interaction networks. The intersecting targets were submitted to the STRING database with the species set to *Homo sapiens* and a minimum confidence score of 0.4. Disconnected nodes were removed to enhance network clarity. The protein–protein interaction (PPI) network was analyzed in Cytoscape using degree, betweenness, and closeness centrality metrics.

Functional enrichment analysis. The biological functions of overlapping genes were further explored using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses in the DAVID bioinformatics system (https://david.ncifcrf.gov/home.jsp). The results were presented for biological processes (BP), molecular functions (MF), cellular components (CC), and pathways involved in vascular development, oxidative stress, and signal transduction regulatory mechanisms.

Experimental verification

Cell culture and treatment. HUVECs were cultured in ECM complete medium (Cat. No. 1001; ScienCell, Carlsbad, CA, USA) within a humidified incubator maintained at 37°C with 5% CO_2 and saturated humidity. The cells were seeded in 96-well plates (Cat. No. 3599; Corning, Corning, NY, USA) with loose-fitting covers for gas exchange. The medium was replaced every 1–2 days. Upon reaching approximately 80% confluence, the cells were passaged using 0.25% trypsin-EDTA (Cat. No. C0201; Beyotime Biotechnology, Shanghai, China).

Drug treatment. After trypsinization, HUVECs were suspended to obtain a calibrated cell suspension at 4×10^5 cells/mL. Then, 100 μL of the cell suspension was added to each well of a 96-well plate (Cat. No. 3599; Corning, Corning, NY, USA) and cultured overnight. On the following day, cells were treated with different concentrations of cisplatin (CAS No. 15663-27-1; Macklin Co., Ltd., Shanghai, China), carboplatin (CAS No. 41575-94-3), and oxaliplatin (CAS No. 61825-94-3). The drug concentrations were as follows: cisplatin at 1, 5, and 10 μmol/L; carboplatin at 10, 20, 40, 80, and 100 μmol/L (five levels); oxaliplatin at 1, 5, and 10 μmol/L (three groups). The control group received no pharmacological intervention. The drugs were prepared according to the procedures described in Refs.[20,21]

CCK-8 assay for cell viability. After 24 and 48 h of treatment, 10 μL of CCK-8 solution (Cat. No. CK04; Dojindo Laboratories, Kumamoto, Japan) was added to each well and incubated for 4 h. Absorbance was measured at 450 nm using a microplate reader (Model Multiskan FC; Thermo Fisher Scientific, Waltham, MA, USA). All assays were performed in triplicate.

Annexin V-FITC/PI apoptosis detection. Apoptosis was assessed using the Annexin V-FITC/PI Apoptosis Detection Kit (Cat. No. KGA108-2; Nanjing KGI Biotechnology Co., Ltd., Nanjing, China). The 10× Binding Buffer was diluted to 1× with distilled water. After trypsin-EDTA digestion (Cat. No. C0201; Beyotime Biotechnology, Shanghai, China), cells were collected by centrifugation at 2000 rpm for 5–10 min at room temperature. The cell pellet was washed once with pre-chilled 1× PBS (Cat. No. C0221A; Beyotime Biotechnology, Shanghai, China) and then centrifuged at 2000 rpm for 5–10 min at 4°C. The cell pellet was resuspended in 300 μL of 1× Binding Buffer. For early apoptosis detection, 5 μL of Annexin V-FITC (Cat. No. KGA108-2; Nanjing KGI Biological, Nanjing, China) was added to the cell suspension and gently mixed. The mixture was incubated in the dark at room temperature for 15 min. Then, 5 μL of propidium iodide (PI) was added, and the samples were incubated for another 5 min before flow cytometric analysis. Finally, 200 μL of 1× Binding Buffer was added to the labeled cells prior to analysis.

RT-qPCR analysis

RNA extraction. Cells were disrupted using TRIzol Reagent (Cat. No. M5102; Xinsaimi Biotechnology Co., Ltd., China) according to the manufacturer's instructions. RNA extraction buffer (0.2 mL per 1 mL of TRIzol reagent) was added, and the mixture was centrifuged at 12,000 rpm for 10 min at 4°C. RNA was isolated from the aque-

ous phase and mixed with an equal volume of 100% ethanol for further processing. The mixture was transferred to NcmSpin Columns (Cat. No. KGA108-2; Nanjing KGI Biological, Nanjing, China) and centrifuged at 12,000*g* for 30 s. The column was washed once with 500 μL of wash buffer (WBT). Finally, the purified mRNA was eluted with RNase-free water and stored at −80°C.

Reverse transcription. To remove genomic DNA, 1 μg of total RNA was incubated with 4 μL of 4× gDNA Wiper Mix (Cat. No. R223; Vazyme, Nanjing, China) at 42°C for 2 min. Reverse transcription was performed using the HiScript II qRT-PCR System (Cat. No. R223; Vazyme, Nanjing, China). The reaction mixture was incubated at 50°C and then heated to 85°C for 5 s. The resulting cDNA was either used immediately for qPCR or stored at −20°C for later use.

qPCR amplification. Quantitative PCR was performed using ChamQ SYBR qPCR Master Mix (Cat. No. Q331-03; Vazyme, Nanjing, China). The reaction mixture (final volume 20 μL) contained 10 μL of 2× master mix, 0.4 μL of each primer (10 μmol/L), 2 μL of cDNA template, and 7.2 μL of ddH_2O. The thermal cycling conditions were as follows: initial denaturation at 95°C for 30 s, followed by 40 cycles of 95°C for 10 s and 60°C for 30 s, and finally, a melting curve analysis was performed. The primer sequences used for amplification were as follows: hACTB_F (CATGTACGTTGCTATCCAGGC), hACTB_R (CTCCTTAATGTCACGCACGAT), hHIF1a_F (AGTCTCGAGATGCAGCCAG), hHIF1a_R (TCACCAGCATCCAGAAGTTT), hNrf2_F (CATCGAGAGCCCAGTCTTC), hNrf2_R (AGTTTGGCTTCTGGACTTGG), hVCAM1_F (CTGTGACCATGACCTGTTCC), hVCAM1_R (AGTCTCCAATCTGAGCAGCA), hICAM1_F (ATGTGCTATTCAAACTGCCCT), hICAM1_R (AATTGGCTCCATGGTGATCT), hNOS3_F (GTCTGATCCACGTGCACAG), hNOS3_R (CCCTTCTCCAGCTGCTCTA).

Results

Descriptive characteristics of AEs

From Q1 2004 to Q4 2024, there were a total of 10,536 reports of VAEs, including: 4483 with carboplatin; 2047 each with cisplatin or oxaliplatin. Table 1 summarizes patient characteristics across these drugs.

Table 1. Baseline characteristics of vascular disorder adverse events associated with platinum-based anticancer drugs.

Characteristics	All platinum-based anticancer drugs	Cisplatin	Carboplatin	Oxaliplatin
Gender, *n* (%)				
Female	5156 (48.94)	760 (37.13)	2836 (63.26)	1560 (38.94)
Male	4450 (42.24)	1124 (54.91)	1244 (27.75)	2082 (51.97)
Unknown	930 (8.82)	163 (7.96)	403 (8.99)	364 (9.09)
Weight (kg), *n* (%)				4006
<80	3173 (30.12)	612 (29.90)	1464 (32.66)	1097 (27.39)
80–100	1167 (11.08)	255 (12.46)	476 (10.62)	436 (10.88)
>100	502 (4.76)	145 (7.08)	214 (4.77)	143 (3.57)
Unknown	5694 (54.04)	1035 (50.56)	2329 (51.95)	2330 (58.16)
Median (kg)	72	73.75	70	73

(Continued)

Table 1. (Continued)

Characteristics	All platinum-based anticancer drugs	Cisplatin	Carboplatin	Oxaliplatin
Age (years), *n* (%)				
<18	272 (2.58)	58 (2.83)	204 (4.55)	10 (0.25)
18–44	729 (6.92)	254 (12.41)	251 (5.60)	224 (5.59)
44–65	4063 (38.56)	791 (38.64)	1603 (35.76)	1669 (41.66)
>65	3407 (32.34)	391 (19.10)	1605 (35.80)	1411 (35.22)
Unknown	2065 (19.60)	553 (27.02)	820 (18.29)	692 (17.28)
Median (years)	63	58	64	63
Occupation of reporters, *n* (%)				
Consumer (CN)	509 (4.83)	131 (6.40)	210 (4.68)	168 (4.19)
Physician (MD)	3293 (31.26)	605 (29.56)	1493 (33.30)	1195 (29.83)
Pharmacist (PH)	1435 (13.61)	140 (6.84)	550 (12.27)	745 (18.60)
Lawer (LW)	9 (0.09)	2 (0.09)	3 (0.07)	4 (0.10)
Other health professional (OT)	4191 (39.78)	680 (33.22)	1782 (39.75)	1729 (43.16)
Unknown	1099 (10.43)	489 (23.89)	445 (9.93)	165 (4.12)
Outcomes, *n* (%)				
Death (DE)	1175 (11.15)	295 (14.41)	531 (11.84)	349 (8.71)
Disability (DS)	116 (1.10)	36 (1.76)	53 (1.18)	27 (0.67)
Hospitalization (HO)	4009 (38.05)	991 (48.41)	1759 (39.24)	1259 (31.43)
Life-Threatening (LT)	1209 (11.47)	139 (6.79)	474 (10.57)	596 (14.88)
Other serious (OT)	3622 (34.38)	519 (25.35)	1477 (32.95)	1626 (40.59)
Required intervention to prevent permanent impairment/damage (RI)	107 (1.02)	19 (0.93)	46 (1.03)	42 (1.05)
Congenital anomaly (CA)	4 (0.04)	/	1 (0.02)	3 (0.07)
Unknown	294 (2.79)	48 (2.35)	142 (3.17)	104 (2.60)
Indication, *n* (%)				
Non-small cell lung cancer	331 (3.12)	100 (4.86)	219 (4.87)	12 (0.29)
Ovarian cancer	856 (8.06)	24 (1.17)	826 (18.35)	6 (0.15)
Lung neoplasm malignant	210 (1.98)	45 (2.19)	152 (3.38)	13 (0.32)
Others	9219 (86.84)	1888 (91.78)	3304 (73.40)	4027 (99.24)

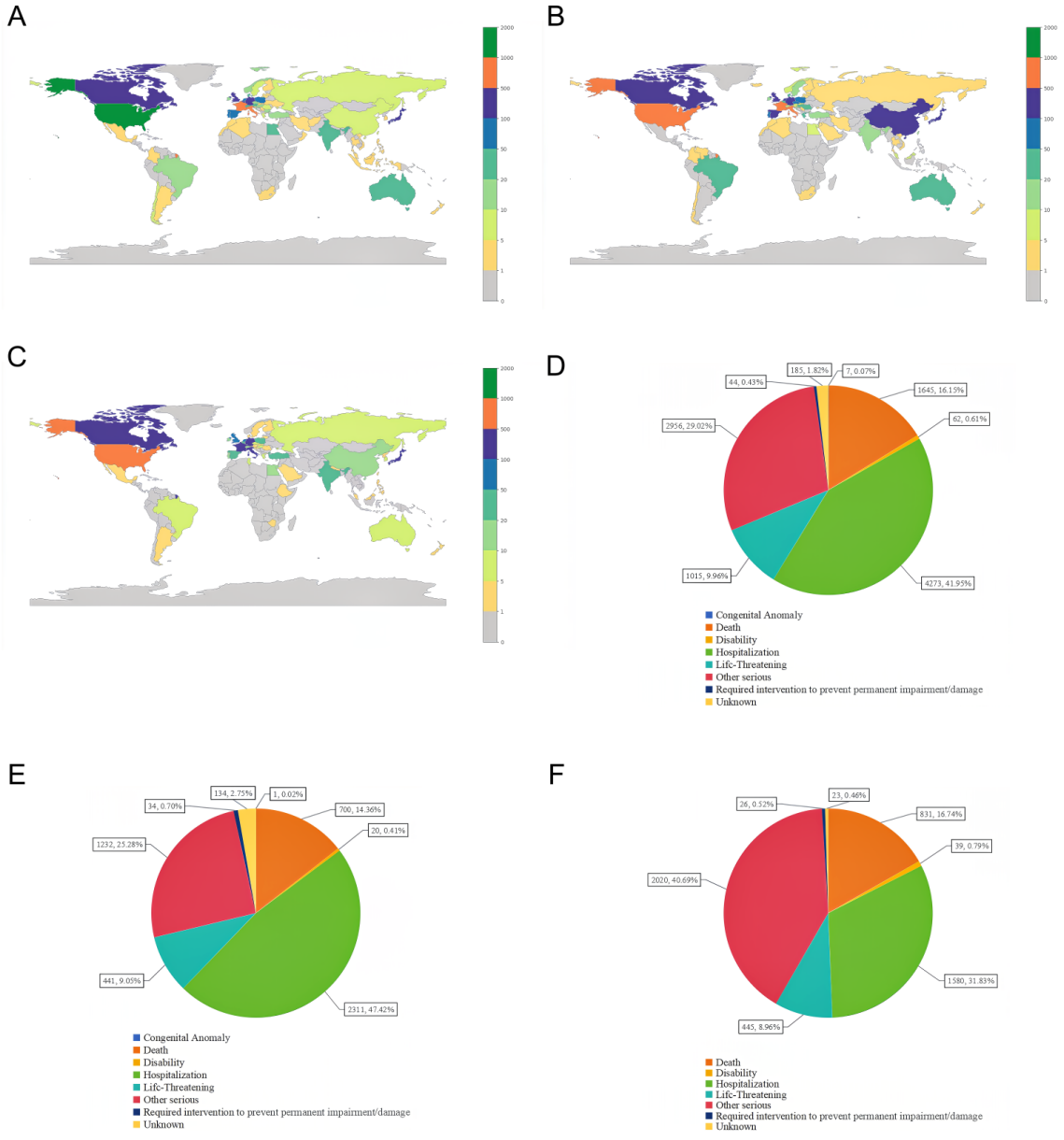

Figure 2. (a–c) Geographic distribution of vascular adverse event reports for carboplatin, cisplatin, and oxaliplatin. (d–f) Clinical outcomes associated with vascular adverse events for each drug.

VAEs predominantly occurred in females (48.94%) and individuals aged 45–65 years (38.56%), with a median age of 63. Most patients had a body weight of less than 80 kg, and the median weight was 72 kg. A significant proportion of reports came from other health professionals (39.78%), followed by physicians (31.25%). Geographic trends showed that AEs related to carboplatin and cisplatin were predominantly reported from the United States, while those for oxaliplatin were mostly from Italy (Figure 2(a)–(c)).

Regarding clinical outcomes (Figure 2(d)–(f)), hospitalization (38.05%) and other important outcomes, such as medically relevant incidents (34.38%), were the most commonly reported. With respect to the therapeutic indications, most of the platinum drugs were prescribed against

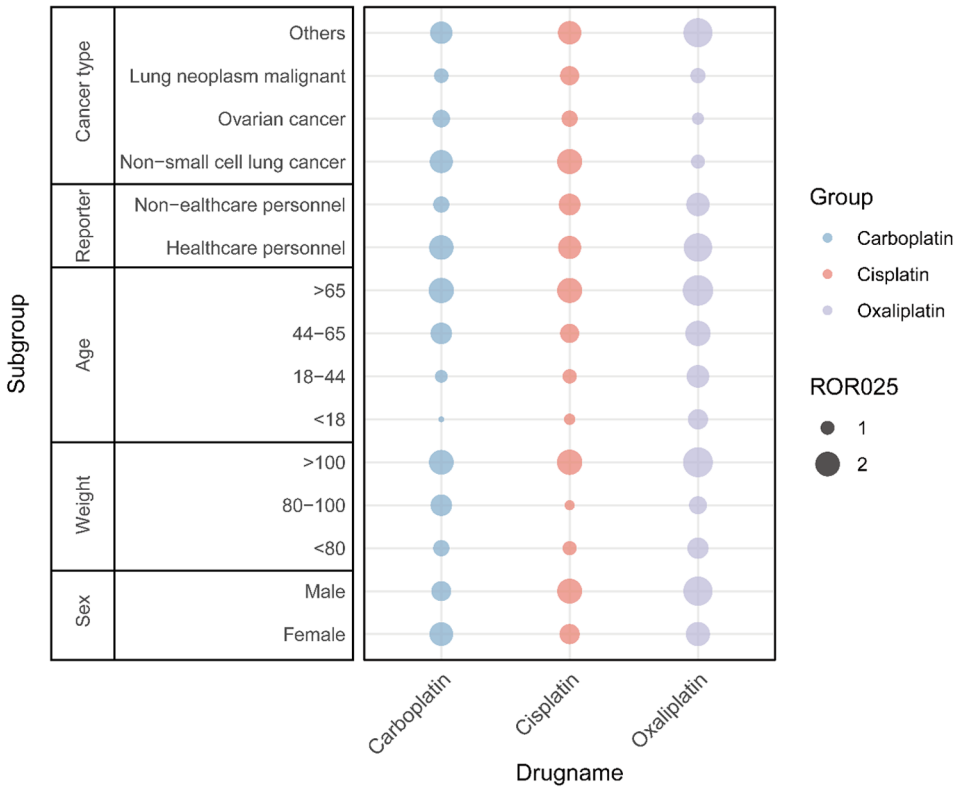

Figure 3. Signal intensity of platinum-based drugs versus vascular AEs by sex, age group, reporter, weight, and cancer type.
AE, adverse event.

ovarian cancer (8.06%), non-small cell lung cancer (3.12%), and obesity (1.47%).

Signal detection analysis

The analysis of the SOC-level disproportionate effect was positive for carboplatin (ROR = 1.67; 95% CI: 1.63–1.72), cisplatin (ROR = 1.72; 95% CI: 1.65–1.79), and oxaliplatin (ROR = 2.05; 95% CI: 1.99–2.11). There may be some indication that all together have a relationship to the vascular disorders in general; Among which, oxaliplatin shows the highest correlation coefficient among these three groups.

The multiple-variable logistic regression analysis was carried out to bring down confounding variables that influence platinum-related VAEs, and the adjusted ratio of risk and CI were calculated. In order to reduce the risk of drug interactions between other medications known for causing vascular adverse reactions, the top 50 frequently used concurrent drugs were compiled in Table S2. According to the fact recognized by the FDA, some drugs include fluorouracil, paclitaxel, bevacizumab, and dexamethasone, all of which may cause vascular toxicity. These suspected drugs were included as covariates in the regression model; other relevant clinical variables were also entered into the model. These findings were similar to the initial analysis, which confirmed that all three platinum agents were significantly associated with VAEs (Table 3). Subgroup analyses also showed consistent safety signals in all the predefined subgroups with sufficient sample sizes (Figure 3).

VAE profiles at the preferred term level

The most frequently reported adverse reactions were identified by analyzing the top 50 preferred terms (PTs) for each drug (Figure 4(a)–(c)). These included hypotension, flushing, hypertension, and deep vein thrombosis. For carboplatin, the most common events were hypotension

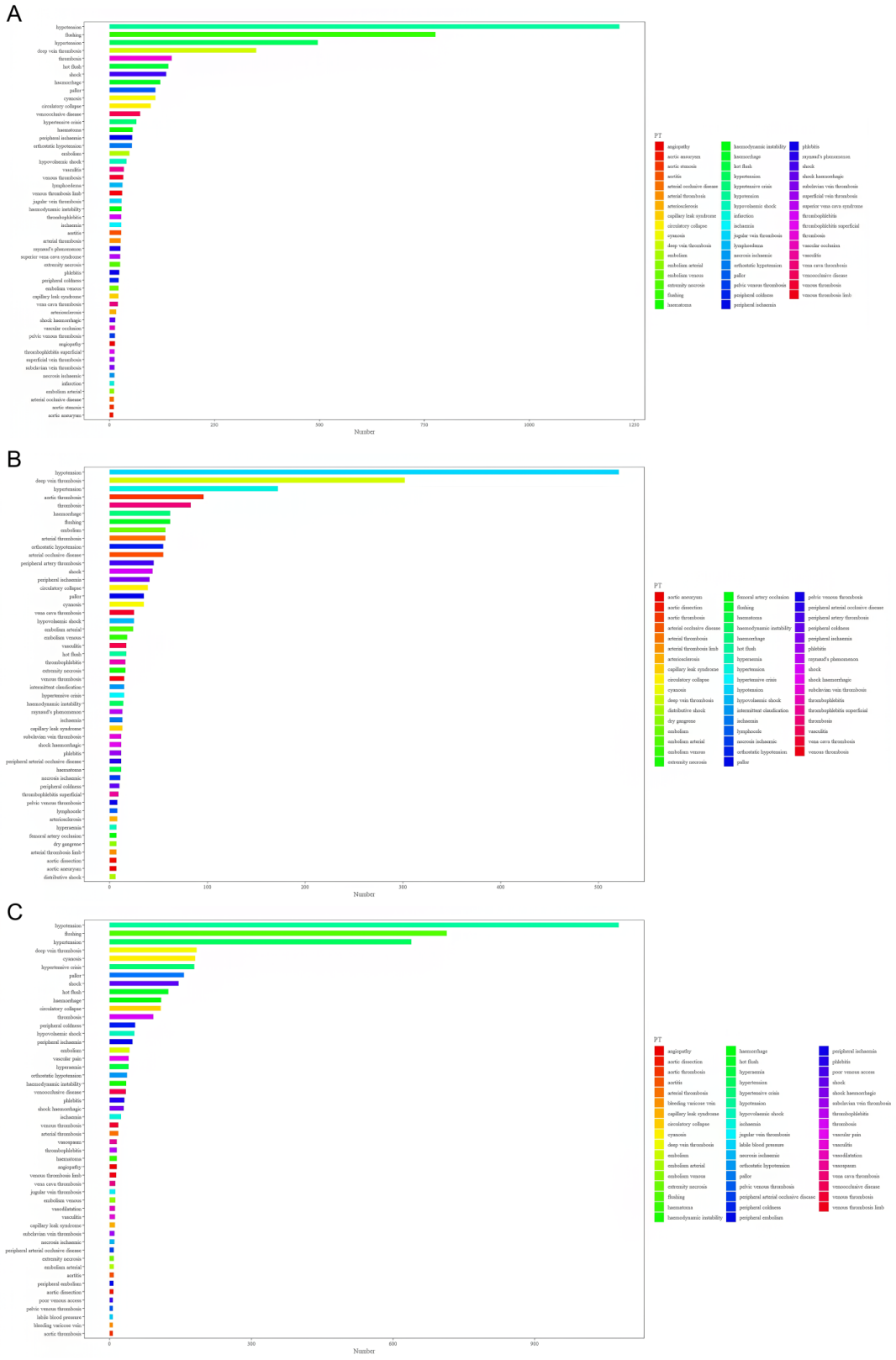

Figure 4. (a–c) Top 50 most frequently reported vascular disorder AEs for carboplatin, cisplatin, and oxaliplatin.
AE, adverse event.

Table 2. Disproportionality signal detection for vascular adverse events associated with platinum-based anticancer drugs.

Platinum-based anticancer	The report number	ROR (95% CI)	PRR (Chi²)	IC (IC025)	EBGM (EBGM05)
Carboplatin	4483	1.67 (1.63, 1.72)	1.65 (1305.50)	0.72 (0.68)	1.65 (1.60)
Cisplatin	2047	1.72 (1.65, 1.79)	1.69 (684.90)	0.76 (0.70)	1.69 (1.62)
Oxaliplatin	4006	2.05 (1.99, 2.11)	2.01 (2393.14)	1.00 (0.96)	2.00 (1.94)

CI, confidence interval; EBGM, empirical Bayesian geometric mean; PRR, proportional reporting ratio; ROR, reporting odds ratio; IC, information component.

($n = 1215$), flushing ($n = 776$), and hypertension ($n = 496$). For cisplatin, reports included deep vein thrombosis ($n = 302$), hypertension ($n = 639$), and aorto-thrombotic events ($n = 96$). For cisplatin, additional cases of deep vein thrombosis ($n = 346$) and hypotension ($n = 521$) were also reported. For oxaliplatin, the most frequent AEs were hypotension ($n = 1078$), flushing ($n = 714$), hypernatremia ($n = 593$), hypertension ($n = 639$), and deep vein thrombosis ($n = 184$). Hypotension was identified as the leading cause of death for all three agents, as confirmed in Tables S3–S5. Disproportionality analysis of PTs yielded 92 positive signals for carboplatin, 80 for cisplatin, and 74 for oxaliplatin, indicating strong associations between these drugs and specific vascular complications. The complete list of positive signals with their corresponding ROR values and 95% CIs is provided in Tables S7 and S8.

Logistic regression analysis

As shown in Tables 2 and 3, most clinical variables were not statistically significant predictors of VAEs for carboplatin. Non-small cell lung cancer is a key confounding factor of cisplatin-associated AEs ($p = 0.004$). Body weight showed a significant association with oxaliplatin-related AE(s) ($p < 0.05$). Therefore, under different clinical conditions and during different periods of the disease, there are obvious adverse reactions in patients.

Modeling time-to-onset and Weibull distribution

The time-to-onset for 15 PTs across all 3 drugs was analyzed (Figure 5). The longest median onset times were Carboplatin: Thrombosis—40.5 days, Cisplatin: Arterial occlusive disease—23.5 days, and Oxaliplatin: Hypertensive crisis—29 days.

The Goodness-of-Fit results are shown in Table S6. The Weibull distribution fits well with treatment durations across all platinum-related vascular toxicity outcomes. All three drugs exhibited an early failure pattern ($\beta < 1$), indicating that most VAEs occurred soon after therapy initiation: Carboplatin: $\beta = 0.73$ (95% CI: 0.70–0.76), Cisplatin: $\beta = 0.90$ (95% CI: 0.84–0.95), and Oxaliplatin: $\beta = 0.77$ (95% CI: 0.74–0.80) (Table 4).

Drug-gene interaction and network pharmacology analysis

We identified 373 target genes for cisplatin, carboplatin, and oxaliplatin using PubChem, UniProt, and the Target Prediction platform. Lung cancer-associated genes ($n = 1523$) were obtained from OMIM and GeneCards. Sixty-three overlapping genes were found between platinum drug targets and lung cancer (Figure 6(a)) and used for downstream analysis.

A dense PPI network, visualized in Cytoscape and constructed using STRING, comprised 62 nodes and 522 edges (Figure 6(b)). GO enrichment analysis (Figure 6(c)) identified the following: BP includes positive regulation of angiogenesis, vasculature development, and oxidative stress response; CC includes membrane raft and plasma membrane microdomain; and MF includes tyrosine kinase activity and protein kinase activity.

Key enriched pathways identified in the KEGG Pathway Analysis (Figure 6(d)) include EGFR tyrosine kinase inhibitor resistance, HIF-1

Table 3. Logistic regression analysis of vascular adverse events associated with platinum-based drugs across clinical variables.

Factors	*p*-Value	Exp(*B*)	95% Confidence interval of Exp(*B*)	
			Lower limit	Upper limit
Carboplatin				
Age	0.558	0.990	0.959	1.023
Body weight	0.637	1.006	0.982	1.030
Sex	0.742	0.829	0.272	2.529
Non-small cell lung cancer	0.890	0.864	0.108	6.898
Ovarian cancer	0.912	1.071	0.319	3.596
Lung neoplasm malignant	0.451	0.450	0.056	3.588
Cisplatin				
Age	0.805	0.997	0.971	1.023
Body weight	0.728	0.997	0.983	1.012
Sex	0.069	0.540	0.278	1.049
Non-small cell lung cancer	0.004	0.242	0.093	0.634
Ovarian cancer	0.999	115933242.178	0.000	/
Lung neoplasm malignant	0.170	0.327	0.066	1.615
Oxaliplatin				
Age	0.206	1.031	0.983	1.082
Body weight	0.025	1.054	1.007	1.104
Sex	0.262	0.380	0.070	2.060
Non-small cell lung cancer	0.147	0.125	0.008	2.069
Ovarian cancer	1.000	7144473.817	0.000	/
Lung neoplasm malignant	0.999	16511859.251	0.000	/

signaling, chronic myeloid leukemia, and vascular remodeling and inflammatory signaling. These results provide molecular evidence that platinum-induced VAEs may be mediated by dysregulation of endothelial function, angiogenesis, and hypoxia signaling.

Experimental verification

To determine treatment settings for subsequent apoptosis and qPCR experiments, we first assessed the effects of cisplatin, carboplatin, and oxaliplatin on cell viability across doses and time points using the CCK-8 assay (Figure 7(a) and (b). For CDDP, the reduction in viability at 24 h was limited, with 10 μM reaching statistical significance ($p < 0.05$). A significant increase in cytotoxicity was observed with higher exposure time, with the 5 and 10 molar amounts becoming significant ($p < 0.05$) and highly significant ($p < 0.001$), respectively. In CBP, the overall ineffective but time-accumulating effect was detected with a significant change at 24 h ($p < 0.05$) and even more so at 48 h ($p < 0.01$).

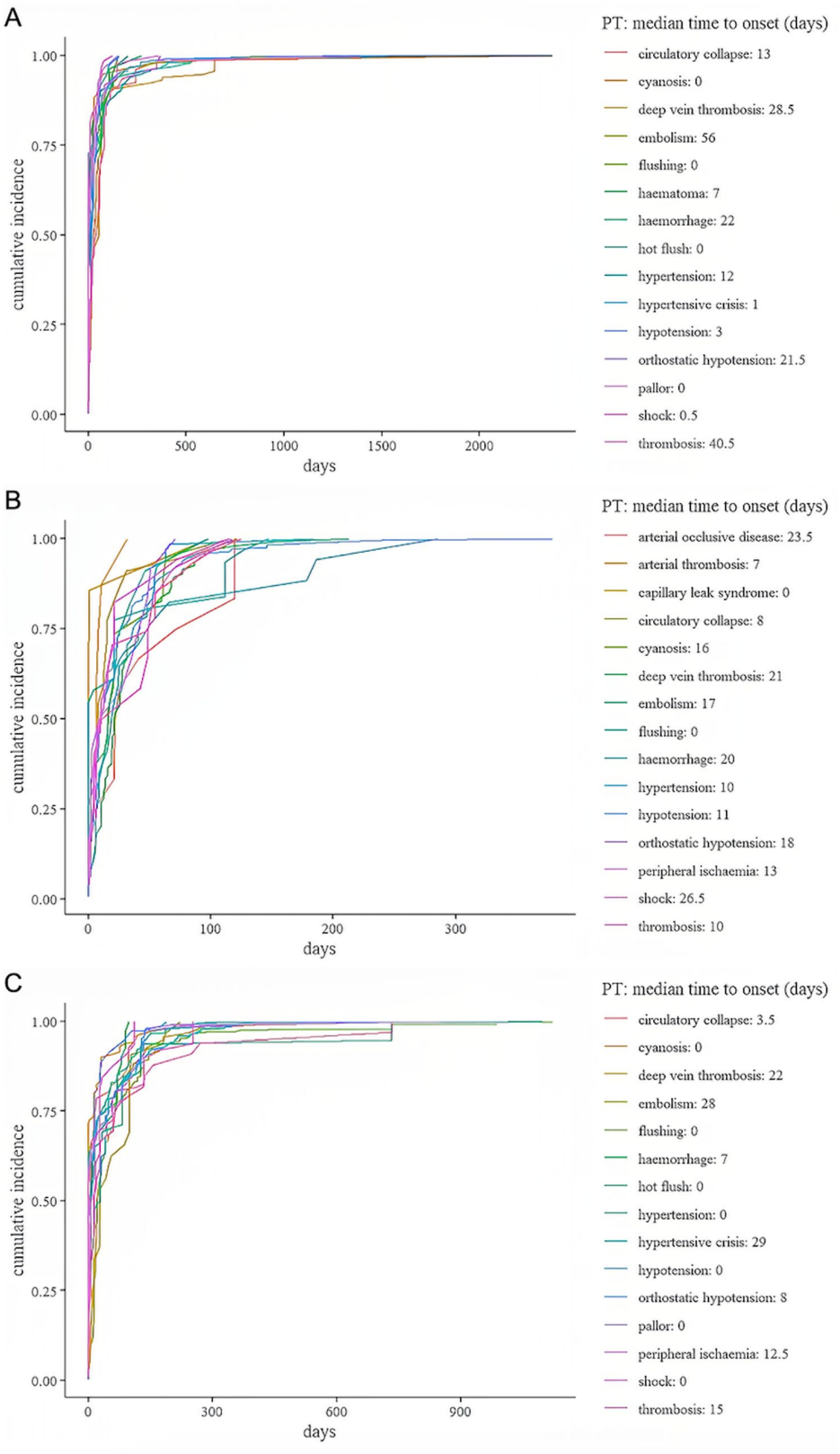

Figure 5. (a–c) Median time-to-onset for vascular adverse events associated with carboplatin, cisplatin, and oxaliplatin.

Table 4. Time-to-onset and Weibull distribution parameters for vascular adverse events related to platinum-based anticancer drugs.

Drug	Time to onset (days)		Weibull distribution		
	Case reports	Median (IQR)	Scale parameter: α (95% CI)	Shape parameter: β (95% CI)	Type
Carboplatin	2045	10 (0–41)	60.27 (55.42–65.12)	0.73 (0.70–0.76)	Early failure
Cisplatin	596	13 (4–36)	31.09 (27.96–34.23)	0.90 (0.84–0.95)	Early failure
Oxaliplatin	2391	1 (0–34)	66.53 (61.45–71.62)	0.77 (0.74–0.80)	Early failure

CI, confidence interval.

On the contrary, OXA was more dose sensitive at 24 h. Both at a rate of 10 and 50 M there were considerable decreases in significance (most significantly $p = 0.001$) for one hundred million, which was highly significant as well($p < 0.0001$). At 48 h, all dose levels of 1–10 μM were still highly significant. Based on the earliest time point with stable parameters and also ensure practicability to downstream functional tests without severe necrosis while maintaining some live cell viability for RNA isolation, we chose CDDP (10 μM × 48 h), CBP (200 μM × 48 h) and OXA (5 μM × 24 h) as unified conditions for apoptosis detection and qPCR.[22–24] The pattern of these CCK-8 tests corresponds to our drug safety signal indicators; Oxaliplatin exhibits a higher rate of cell death compared to other drugs at shorter times, corresponding to the highest risk of vascular complications based on real-world data, while cisplatin and carboplatin have relatively lower risks due to slower response.

Apoptosis was quantified by flow cytometry with stage-specific readouts (Figure 7(c)–(e)). Early apoptosis was 1.13% in the control and was 1.03% with cisplatin 5 μM (no appreciable change vs control), 2.98% with carboplatin 200 μM (absolute increase of +1.85 percentage points; approximately 2.6-fold of control), and 2.42% with oxaliplatin 1 μM (+1.29 points; approximately 2.1-fold) (Figure 7(c)). Late apoptosis or secondary necrosis was 1.13% in the control and increased to 6.02% with cisplatin (+4.89 points; approximately 5.3-fold), 9.99% with carboplatin (+8.86 points; approximately 8.8-fold), and 6.43% with oxaliplatin (+5.30 points; approximately 5.7-fold) (Figure 7(d)). Total apoptosis was as follows: 2.26% in the Control group, increasing by 4.79 points to about 7.05%, which is a 3.1-times increase after using cisplatin (±oxaliplatin/carboplatin); The highest increase reached nearly 10% at carboplatin dosage. Collectively, all treatments increased apoptosis and reduced the viable fraction, with the overall magnitude ranking carboplatin > oxaliplatin > cisplatin; oxaliplatin showed a comparatively greater contribution from early apoptosis, whereas cisplatin was characterized by a predominance of late apoptosis.

In our flow cytometry assay, carboplatin produced the largest increase in total apoptosis at the tested settings, whereas oxaliplatin contributed a higher fraction of early apoptosis. These trends are directionally consistent with an earlier response to oxaliplatin, while absolute magnitudes differ across systems and endpoints.

FAERS discrepancy suggested associations among all three platinum drugs (oxaliplatin) and VAEs; oxaliplatin had a stronger correlation, and such events tended to appear earlier during treatment initiation. Network analysis showed pathways involving oxidative stress, endothelial function, and the HIF-1/EGFR signaling pathway.

In RT-qPCR, NOS3 shows no significant differences among groups (Figure 7(f)). The mean NOS3 level increases with cisplatin versus control, but this increase is not significant. Nrf2 decreases with oxaliplatin versus control ($p < 0.05$), while cisplatin and carboplatin versus control are not significant (Figure 7(g)). VCAM1 decreases with oxaliplatin versus control, cisplatin, and carboplatin ($p < 0.001$ for all comparisons); cisplatin versus control is not significant (Figure 7(h)). ICAM1 increases with cisplatin

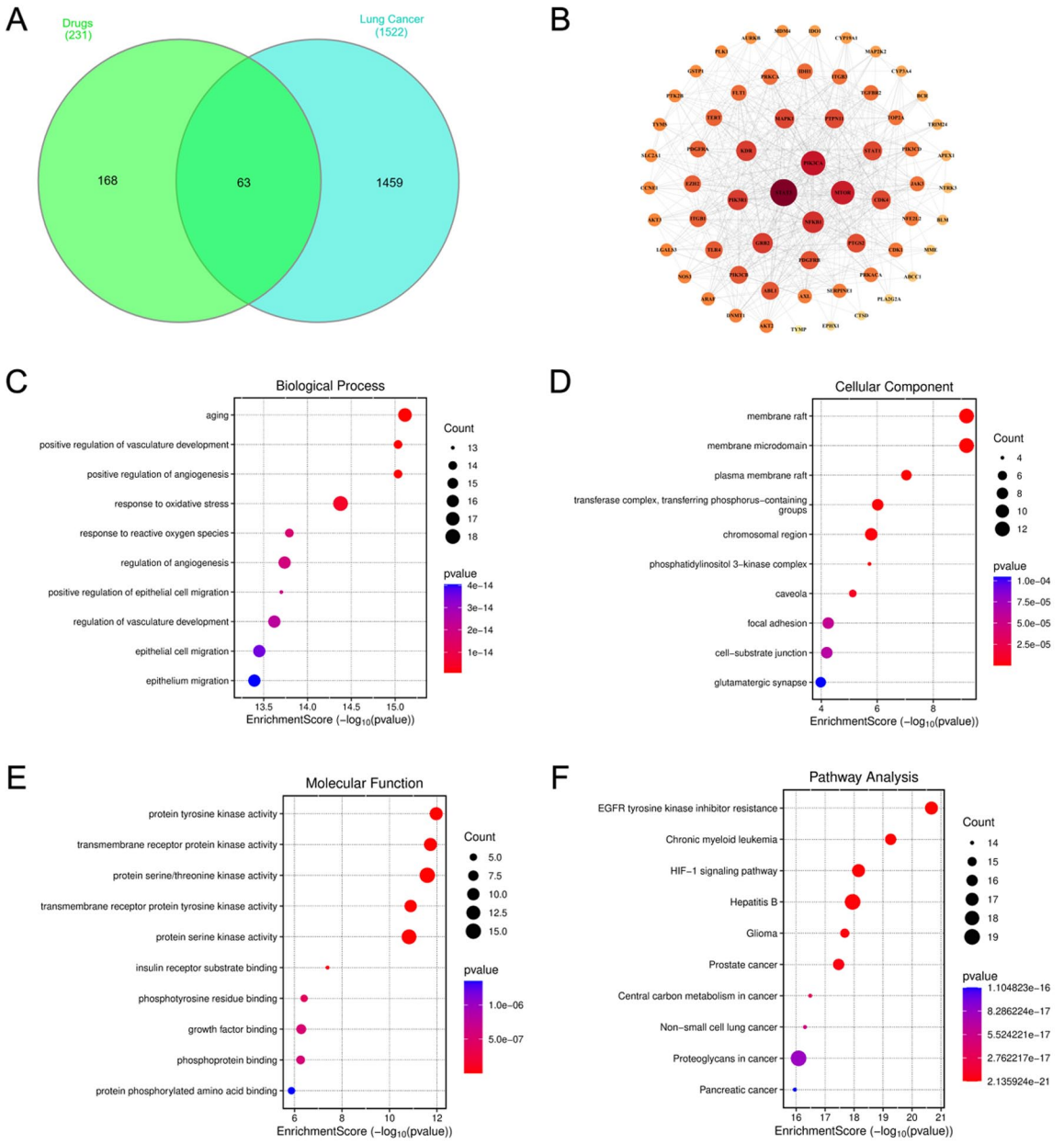

Figure 6. (a) Venn diagram showing overlapping genes between platinum-based drugs and lung cancer targets. (b) PPI network of overlapping targets. (c–e) GO enrichment analysis (BP, CC, MF). (f) KEGG pathway enrichment of intersecting genes.
BP, biological processes; CC, cellular component; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; MF, molecular function; PPI, protein–protein interaction.

versus control ($p < 0.05$–0.01). Carboplatin versus control shows no significant change. Oxaliplatin shows a mean increase versus control, but the difference is also not significant (Figure 7(i)). HIF1A shows no significant differences across treatments, although the group means increase relative to the control without reaching significance (Figure 7(j)).

In summary, the pharmacovigilance and network data and these RT-qPCR results show that there is a decrease in the antioxidant trans-factor (Nrf2)

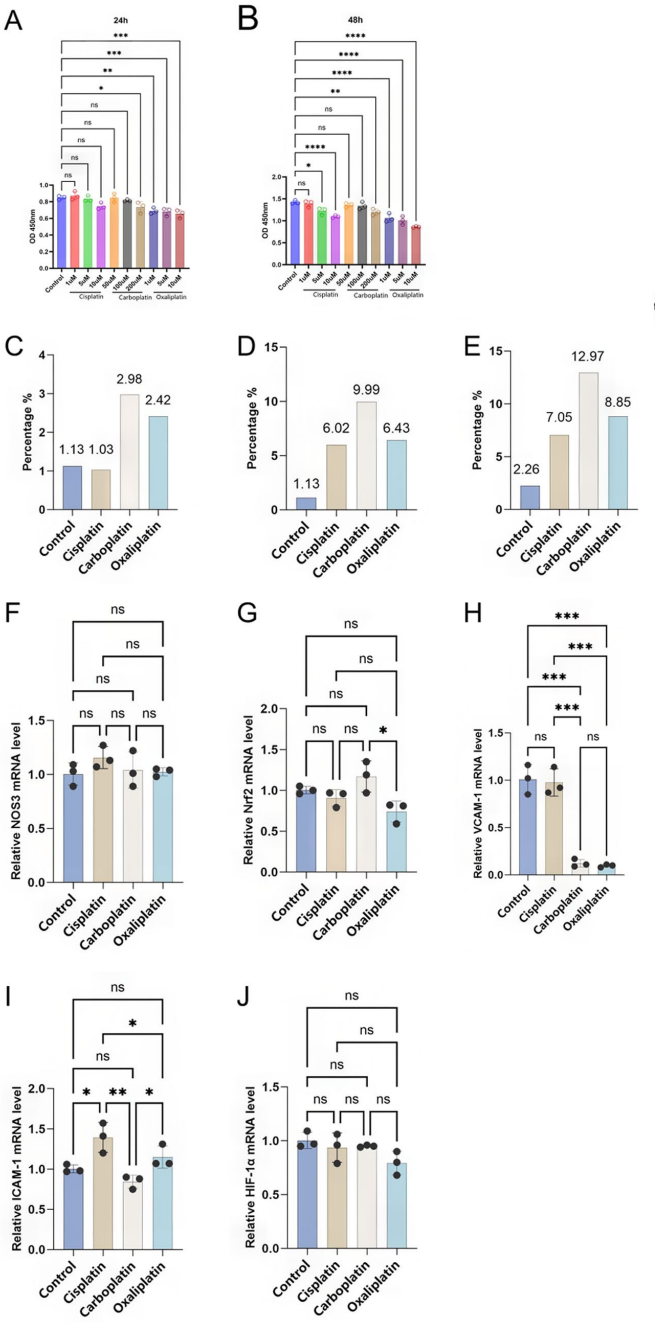

Figure 7. CCK-8 assessment of cell viability at 24 h and 28 h for three platinum agents and three dose levels, Annexin V FITC/PI flow cytometry of apoptosis, and RT-qPCR analysis of endothelial and stress related genes. (a) Shows 24 h and (b) shows 48 h. Each panel includes CDDP, CBP, and OXA, each tested at low, medium and high dose levels. Results are displayed as mean values from at least three independent experiments with at least three technical wells per condition. Colors or marker shapes distinguish drugs, and fill or line styles distinguish dose levels, as indicated in the figure key. (c) Early apoptosis. (d) Late apoptosis. (e) Total apoptosis (early plus late). Bars represent the mean percentage of cells for Control, cisplatin 5 μM, carboplatin 200 μM, and OXA 1 μM. Early apoptosis was defined as Annexin V FITC positive and PI negative, and late apoptosis as Annexin V FITC positive and PI positive. Show relative mRNA levels for (f) NOS3, (g) Nrf2, (h) VCAM1, (i) ICAM1 and (j) HIF1A across Control, cisplatin, carboplatin and OXA. Bars indicate mean ± SEM and each dot represents an independent experiment.

Statistical analysis was performed using one way ANOVA with post hoc multiple comparisons was used.
Significance thresholds: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, ns, not significant.
CBP, carboplatin; CDDP, cisplatin; OXA, oxaliplatin; PI, propidium iodide.

associated with oxaliplatin, an increase of endothelial-adhesion-molecule ICAM1 with cisplatin. However, HIF1A and NOS3 are not significantly changed at present.

Discussion

The results show that all three agents are significantly correlated with VAEs. Among them, oxaliplatin exhibits the highest correlation, with a ROR of 2.05 (95% CI: 1.99–2.11). Additionally, the Weibull shape coefficient β is less than 1 for all three drugs, indicating that early failures (vascular complications) are more likely to occur during the initial phase of treatment. At the PT level, hypotension, flushing, hypertension, and venous thrombosis are commonly observed reactions.

Our RT-qPCR findings partially aligned with the pharmacovigilance signals and network-inferred mechanisms. Specifically, oxaliplatin markedly decreased Nrf2 activity; Cisplatin increased the level of ICAM1 through this pathway under oxidative stress or endothelial activation conditions. These observations support the involvement of Nrf2-mediated antioxidant defense and ICAM-1-mediated adhesion in platinum-induced vascular injury. The Nrf2/HO-1 axis is a central regulator of endothelial antioxidant and anti-inflammatory responses; its dysfunction can promote inflammation and enhance endothelial-leukocyte interaction.[25–27] ICAM-1, in turn, plays a key role in endothelial gap formation and cytoskeletal reorganization.[28]

However, some of these phenomena did not match the predictions. No significant change in HIF1A levels among different drug treatments within the tested condition; NOS3 also showed no obvious difference between Groups. Moreover, VCAM1 was significantly decreased by oxaliplatin, which contrasts with the pro-inflammatory adhesion narrative typically associated with endothelial dysfunction. These discrepancies may be explained by several factors: (1) the single time-point measurement may have missed dynamic or transient changes in gene expression, particularly for HIF-1, which is known to exhibit time-dependent and biphasic responses[29–31]; (2) endothelial cells may regulate VCAM1 and ICAM1 through distinct signaling pathways, and oxaliplatin could preferentially affect VCAM1 expression via mechanisms unrelated to inflammation; and (3) the in vitro conditions (static culture, single cell type) cannot fully recapitulate the complex in vivo microenvironment where multiple cell types and shear stress modulate gene expression.

Thus, our results suggest that platinum-induced vascular toxicity involves multiple, pathway-specific mechanisms rather than a uniform oxidative-inflammatory cascade. While the Nrf2-ICAM1 axis appears to contribute to oxaliplatin- and cisplatin-associated injury, respectively, other pathways (e.g., HIF-1, NOS3) may play context-dependent roles that require further investigation with refined experimental designs. The network pharmacology analysis enriched pathways, such as HIF-1 and EGFR signaling, which have been implicated in endothelial injury and repair.[12,13] Although HIF1A was not significantly changed at the sampled time point, its role may be more prominent in later remodeling or under hypoxic conditions.[29–31]

The early failure pattern observed in this study aligns with clinical reports of acute vascular events during platinum-based therapy, such as coronary artery spasm, conduction abnormalities, and hemodynamic disturbances. For example, oxaliplatin has been associated with third-degree atrioventricular block and coronary spasm, underscoring the need for close monitoring during initial treatment cycles.[8] Oxaliplatin may cause portal hypertension and sinusoidal obstruction syndrome. During the course of administration, it will appear at any time as endothelial damage leads to sinusoidal fibrosis.[32,33]

Logistic regression analysis showed that different effects on blood vessels under various drugs; patients' disease conditions were influenced by their body weight and types of cancer in many ways. Notably, non-small cell lung cancer was a significant confounder for cisplatin-related VAEs, while body weight was significantly associated with oxaliplatin-related VAEs. Based on the above results, personalization enhances risk assessment. Co-administration of other therapies that increase vascular permeability, such as anti-angiogenic agents and taxanes for chemotherapy. There may be an increased risk of AEs because they work well together.[34,35]

From a clinical perspective, the early onset pattern supports enhanced cardiovascular surveillance during the first few cycles of platinum-based treatment, including blood pressure monitoring,

electrocardiography, and thrombotic risk assessment. In patients with pre-existing endothelial dysfunction or metabolic syndrome, more frequent monitoring and preventive strategies (e.g., ambulatory blood pressure monitoring, D-dimer screening) should be considered. Oxaliplatin can induce a portosystemic shunt, such as splenomegaly, thrombocytopenia, and portal vein tumor thrombus, during its use.[36]

Limitations

Several limitations of this study must be acknowledged. FAERS is an unverified reporting system that collects spontaneously reported AEs, which may contain incomplete information or be subject to selective reporting. Therefore, no causal relationship can be confirmed between platinum-based drugs and vascular adverse reactions using this dataset alone. Additionally, several essential clinical indicators are missing from the documentation, such as drug dosages, total treatment durations, patients' cardiac risk status before medication administration, therapeutic agents co-administered simultaneously, and other related data that significantly affect the later-stage multivariate regression models. Third, although the Weibull model predicts an early failure pattern for all three drugs, time-to-onset data are available for only a subset of cases, and variations in PT classification may affect the outcomes. Fourth, under static in vitro culture conditions with low shear stress, the single HUVEC model may differ from the three-dimensional microenvironment of the vascular network in vivo, which contains more diverse physicochemical signals. Gene expression analysis is performed at a single time point and may fail to capture the dynamic changes of key pathways, such as HIF-1 signaling. Fifth, due to the reliance on database annotations and computational algorithms in network pharmacology prediction, there may be target bias or false-positive results, which require further validation using functional assays and animal experiments. Sixth, the definition of VAEs based on the MedDRA SOC level classification may encompass clinically and pathophysiologically heterogeneous conditions, such as thrombotic events (e.g., deep vein thrombosis), vasomotor disturbances (e.g., hypotension and flushing), and inflammatory conditions (e.g., vasculitis). Although this broad definition was intentionally selected to enhance the sensitivity of first-generation signal detection in this exploratory study, it may lead to signal dilution or exaggeration of certain event types. This issue is explicitly noted as a source of heterogeneity in the "Methods" section. Future studies using finer-grained event criteria based on shared pathophysiological mechanisms (e.g., thromboembolic vs hemodynamic events) will help refine and expand these findings. Finally, the study relies on a single data source with a limited geographic scope, primarily covering the United States and Europe, and few related studies are available from other regions, including China. Despite these limitations, the integration of real-world pharmacovigilance data, network pharmacology, and in vitro experiments provides a multidisciplinary understanding of platinum-induced vascular toxicity.

Conclusion

The entire process comparison of vascular adverse outcomes between cisplatin, carboplatin, and oxaliplatin is presented herein. All three drugs were significantly linked to vascular events, with an early-onset pattern suggestive of acute endothelial injury, and oxaliplatin exhibited the strongest signal and the shortest TTO. Integration of pharmacovigilance data, network pharmacology, and in vitro experiments suggests that oxidative stress and endothelial activation contribute to platinum-induced vascular toxicity, as evidenced by the downregulation of Nrf2 (oxaliplatin) and upregulation of ICAM1 (cisplatin). However, the absence of significant changes in HIF1A and NOS3, and the unexpected decrease in VCAM1 with oxaliplatin, indicate that the underlying mechanisms are complex and pathway-specific rather than a uniform oxidative-inflammatory cascade. These findings underscore the importance of early cardiovascular monitoring during platinum-based treatment and highlight the potential of Nrf2-targeted protective strategies. Future studies incorporating longitudinal biomarker assessment, dynamic pathway profiling, and more physiologically relevant models are warranted to fully elucidate the temporal and mechanistic landscape of platinum-associated vascular injury.

Declarations

Ethics approval and consent to participate

Based on publicly accessible data in the FDA Adverse Event Reporting System (FAERS), which includes full-anonymized and de-identified information. Based on the policy requirements of this

entity and according to the principle of the Declaration of Helsinki, ethics review and informed consent were not necessary in carrying out a secondary analysis involving publicly accessible de-identification information. Therefore, there was no institution of an IRB and no patient consent.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form (including individual details, images, or videos), and all data used are from a publicly available anonymized database. Therefore, consent for publication was not required.

Author contributions

Yuzhu Chen: Investigation; Resources; Writing – original draft.

Chunhua Wang: Data curation; Resources.

Peng Jiang: Writing – original draft.

Yida Chen: Writing – review & editing.

Tongmei Zhang: Conceptualization; Funding acquisition.

Shanshan Cai: Data curation; Resources; Validation.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data underlying this study are available from the FDA Adverse Event Reporting System (FAERS) database, which is publicly accessible at: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The analyzed datasets generated during the study are available from the corresponding author* upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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