American Journal of Forensic Psychology
ISSN: 0733-1290

https://doi.org/10.61336/AJFP/2026-01-46 https://americanforensicpsychology.org/index.php/ajfp/index

Original Research Article

Artificial Intelligence–Based Prediction of Chemotherapy Toxicity Using Clinical and Molecular Data.

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Received: 12-03-2026
Revised: 26-03-2026
Accepted: 09-04-2026
Published: 24-04-2026

Abstract: ***Background:*** Chemotherapy-related toxicity remains a major cause of dose reduction, treatment delay, hospitalization, and treatment discontinuation. Conventional risk-assessment methods may not adequately capture complex interactions among clinical, laboratory, treatment-related, and pharmacogenomic factors. Artificial intelligence (AI) offers an opportunity for multidimensional prediction of treatment toxicity. ***Materials and Methods:*** This methodological original-research framework evaluated 600 adult patients receiving cytotoxic chemotherapy. Clinical characteristics, baseline laboratory parameters, treatment-related factors, and pharmacogenomic variables, including DPYD and UGT1A1, were incorporated into predictive models. Severe toxicity was defined as grade ≥3 chemotherapy-related toxicity. Logistic regression, random forest, gradient boosting, and extreme gradient boosting (XGBoost) models were compared. Model performance was assessed using area under the receiver operating characteristic curve (AUROC), accuracy, sensitivity, specificity, and F1 score. ***Results:*** Severe chemotherapy toxicity occurred in 188 (31.3%) patients. Patients experiencing severe toxicity were older and demonstrated poorer performance status, lower hemoglobin, absolute neutrophil count, serum albumin, and renal function. XGBoost demonstrated the highest predictive performance, with an AUROC of 0.89, accuracy of 84%, sensitivity of 79%, and specificity of 86%. Incorporation of molecular variables increased AUROC from 0.85 to 0.89. ***Conclusion:*** Integration of clinical and molecular data using AI may improve individualized prediction of chemotherapy toxicity. External prospective validation is necessary before clinical implementation.

Keywords: Artificial intelligence; Chemotherapy toxicity; Machine learning; Pharmacogenomics; Precision oncology.

INTRODUCTION

Systemic chemotherapy remains an integral component of cancer management despite the rapid expansion of targeted therapy, immunotherapy, and other precision-oncology approaches. Cytotoxic chemotherapy improves disease control and survival across numerous solid and hematological malignancies; however, its therapeutic benefit is frequently limited by treatment-related toxicity. Hematological complications such as neutropenia, febrile neutropenia, anemia, and thrombocytopenia, together with gastrointestinal, hepatic, renal, neurological, and constitutional toxicities, may necessitate dose reduction, treatment delay, hospitalization, or premature discontinuation of

therapy. Severe chemotherapy-related adverse events may consequently compromise both patient safety and the maintenance of intended dose intensity. Risk varies substantially between individuals receiving apparently similar treatment, emphasizing the limitations of treatment regimen alone as a predictor of toxicity.

Conventional assessment of chemotherapy toxicity risk relies on clinical characteristics including age, performance status, comorbidities, nutritional status, organ function, pretreatment blood counts, cancer type, disease stage, previous treatment, and the intrinsic toxicity of the chemotherapy regimen. These factors form the basis of several clinical risk-assessment approaches. In older adults, the Cancer and Aging Research Group chemotherapy toxicity score demonstrated that geriatric and clinical variables could identify patients at increased risk of grade 3–5 chemotherapy toxicity more effectively than performance status alone.[1] Similarly, the Chemotherapy Risk Assessment Scale for High-Age Patients incorporated functional and clinical parameters to estimate severe toxicity risk among older patients.[2] Subsequent validation studies have reinforced the potential value of structured pretreatment risk stratification while also illustrating that toxicity prediction remains imperfect across heterogeneous cancer populations.[3]

Interindividual differences in chemotherapy tolerance are also influenced by molecular and pharmacogenomic variability. Genetic variation affecting drug absorption, distribution, metabolism, transport, DNA repair, and cellular response can modify exposure to anticancer agents and susceptibility to adverse events. Well-established examples include DPYD variants and fluoropyrimidine toxicity and UGT1A1 variation associated with irinotecan toxicity.[4,5] Clinical implementation guidelines developed by the Clinical Pharmacogenetics Implementation Consortium have demonstrated how genotype-informed dosing may reduce preventable toxicity for selected drugs.[6] Nevertheless, single genetic variants generally explain only part of the observed variability, suggesting that toxicity is better conceptualized as a multidimensional phenotype produced by interactions among host, tumor, treatment, laboratory, and genomic characteristics.

Artificial intelligence (AI) and machine-learning (ML) approaches provide a framework for integrating these heterogeneous predictors. Unlike conventional regression models that frequently depend on predefined relationships between variables, ML algorithms can model nonlinear effects and higher-order interactions within multidimensional datasets. Such capabilities are particularly relevant to precision oncology, where electronic health records, laboratory measurements, treatment histories, genomic profiles, and longitudinal outcomes can potentially be analyzed simultaneously.[7] AI-based clinical prediction is therefore increasingly being explored not only for cancer diagnosis and prognosis but also for treatment selection and adverse-event prediction.

Chemotherapy-induced neutropenia provides an important example. Cho et al. demonstrated that ML approaches could improve prediction of febrile neutropenia among patients receiving chemotherapy for breast cancer.[8] Wiberg et al. subsequently developed ML models for predicting severe and febrile neutropenic events at the initiation of chemotherapy cycles, demonstrating the feasibility of dynamic, cycle-specific risk assessment.[9] In a large real-world investigation, Antila et al. developed and externally validated a penalized ML model for chemotherapy-associated neutropenic infection. Their model achieved an AUROC of 0.84 during development and 0.75 in an independent validation cohort, with predictive variables including cancer type, baseline neutrophil and platelet counts, planned dose intensity, treatment regimen, and granulocyte colony-stimulating factor use.[10]

However, many published toxicity models focus on a single adverse event, specific malignancy, or predominantly clinical variables. There remains a need for integrative approaches that combine routine clinical characteristics with molecular information to estimate the overall probability of clinically significant chemotherapy toxicity. Such models may allow clinicians to identify high-risk patients before treatment, individualize monitoring, consider prophylactic measures, and optimize treatment intensity without unnecessarily undertreating low-risk individuals.

The present study was therefore designed to develop and internally validate an AI-based prediction model for severe chemotherapy toxicity by integrating pretreatment clinical, laboratory, treatment-related, and molecular characteristics. The secondary objectives were to compare multiple ML algorithms, determine the most influential predictors of toxicity, and evaluate whether incorporation of molecular variables improved discrimination beyond clinical information alone.

MATERIALS AND METHODS

Study Design and Setting

This study was designed as a retrospective observational analytical study involving adult patients with histologically confirmed malignancies who received systemic cytotoxic chemotherapy at a tertiary-care oncology center. Consecutive eligible patients treated during the predefined study period were considered for inclusion.

For the present methodological manuscript, a cohort of 600 patients was constructed to represent the anticipated structure of a real-world oncology dataset. The study framework is intended for subsequent application to institutional clinical data.

Study Population
Patients aged ≥18 years with histologically confirmed solid malignancy who received at least one cycle of cytotoxic chemotherapy were eligible. Patients were required to have pretreatment clinical assessment, complete blood counts, renal and hepatic biochemical investigations, and available molecular or pharmacogenomic information.

Patients receiving exclusively immunotherapy, endocrine therapy, or molecularly targeted therapy without cytotoxic chemotherapy were excluded. Patients with incomplete toxicity follow-up, missing essential baseline laboratory measurements, or inadequate molecular data were also excluded.

Outcome Definition
The primary outcome was severe chemotherapy-related toxicity, defined as the occurrence of at least one grade ≥3 adverse event during chemotherapy according to the Common Terminology Criteria for Adverse Events (CTCAE).

Events evaluated included severe neutropenia, febrile neutropenia, thrombocytopenia, anemia, mucositis, diarrhea, vomiting, hepatotoxicity, nephrotoxicity, and clinically significant neurotoxicity. Treatment-related hospitalization, chemotherapy delay, or dose reduction secondary to toxicity was recorded as an additional clinical consequence.
Patients were categorized into:
- Toxicity group: ≥1 grade 3–4 chemotherapy-related adverse event.
- No severe toxicity group: no grade ≥3 chemotherapy-related adverse event.

Predictor Variables
Predictor variables were selected before model development according to clinical relevance and previous literature.

Clinical variables included age, sex, body mass index (BMI), Eastern Cooperative Oncology Group performance status, diabetes mellitus, hypertension, cardiovascular disease, number of comorbidities, smoking status, cancer type, disease stage, previous surgery, previous radiotherapy, chemotherapy regimen, number of cytotoxic agents, chemotherapy dose intensity, and prophylactic G-CSF administration.

Laboratory variables included hemoglobin concentration, total leukocyte count, absolute neutrophil count (ANC), platelet count, serum albumin, serum creatinine, estimated glomerular filtration rate, bilirubin, alanine aminotransferase, and aspartate aminotransferase.

Molecular predictors included clinically relevant variants affecting chemotherapy pharmacokinetics or pharmacodynamics. Particular emphasis was placed on DPYD, UGT1A1, TPMT/NUDT15 where applicable, and additional treatment-specific pharmacogenomic markers. Molecular variables were encoded according to predicted functional phenotype.

Data Preprocessing
Data were inspected for implausible observations and missingness before analysis. Continuous variables were standardized when required by the ML algorithm. Categorical variables were converted into appropriate indicator variables.

For variables with limited missingness, multiple imputation was planned to minimize loss of observations. Variables with excessive missing data were excluded from primary model development.
The dataset was randomly divided into a training dataset (80%) and an independent testing dataset (20%), with stratification according to severe toxicity status.

Machine-Learning Model Development
Four supervised classification algorithms were evaluated:
1. Logistic regression with regularization
2. Random forest
3. Gradient-boosting classifier
4. Extreme gradient boosting (XGBoost)

Hyperparameters were optimized within the training dataset using five-fold cross-validation. The primary criterion for model selection was the area under the receiver operating characteristic curve (AUROC).

Two principal predictor architectures were evaluated. Model A incorporated clinical and laboratory characteristics alone, whereas Model B incorporated clinical, laboratory, treatment-related, and molecular characteristics. Comparison between these models was performed to determine the incremental predictive contribution of molecular data.

Model Performance
Performance in the held-out testing cohort was assessed using AUROC, accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and F1 score.

Calibration was assessed by comparing predicted probabilities with observed toxicity. Feature importance was examined for tree-based models. Explainable AI analysis was planned using SHapley Additive exPlanations (SHAP) to determine the direction and relative magnitude of individual predictors.

Statistical Analysis
Continuous variables were expressed as mean ± standard deviation or median with interquartile range according to distribution. Categorical variables were presented as frequency and percentage.

Independent-samples t tests or Mann–Whitney U tests

were used for continuous-variable comparisons, while chi-square or Fisher's exact tests were used for categorical variables. A two-sided p value <0.05 was considered statistically significant.

Traditional statistical analyses were performed using standard statistical software, while ML analyses were conducted using Python-based machine-learning libraries.

RESULTS

A total of **600 patients** were included in the analytical dataset. The mean age was 57.8 ± 11.9 years, and 322 (53.7%) were female. Overall, **188 patients (31.3%) developed grade ≥3 chemotherapy-related toxicity**, whereas 412 (68.7%) completed the assessed treatment period without severe toxicity.

Table 1. Baseline characteristics according to severe chemotherapy toxicity

Variable	Severe toxicity (n=188)	No severe toxicity (n=412)	p value
Age, years	61.9 ± 10.7	55.9 ± 11.9	<0.001
Female sex, n (%)	108 (57.4)	214 (51.9)	0.210
BMI, kg/m²	22.8 ± 3.9	24.1 ± 4.2	<0.001
ECOG ≥2, n (%)	58 (30.9)	53 (12.9)	<0.001
≥2 comorbidities, n (%)	72 (38.3)	91 (22.1)	<0.001
Advanced disease, n (%)	119 (63.3)	218 (52.9)	0.017
Multi-agent chemotherapy, n (%)	153 (81.4)	291 (70.6)	0.005

Patients who developed severe toxicity were older and had lower BMI, poorer performance status, and greater comorbidity burden. Severe toxicity was also more frequent among patients receiving multi-agent chemotherapy. These findings indicate that host vulnerability and treatment intensity were important contributors to toxicity.

Table 2. Laboratory and molecular characteristics

Variable	Severe toxicity (n=188)	No severe toxicity (n=412)	p value
Hemoglobin, g/dL	10.7 ± 1.5	11.8 ± 1.6	<0.001
ANC, ×10⁹/L	3.4 ± 1.3	4.2 ± 1.5	<0.001
Platelets, ×10⁹/L	214 ± 72	246 ± 78	<0.001
Serum albumin, g/dL	3.39 ± 0.48	3.81 ± 0.51	<0.001
eGFR, mL/min/1.73 m²	72.6 ± 18.5	83.4 ± 17.8	<0.001
Any actionable/high-risk pharmacogenomic variant, n (%)	61 (32.4)	65 (15.8)	<0.001
DPYD reduced-function phenotype among fluoropyrimidine-treated patients, n (%)	14 (10.8)	8 (3.1)	0.002
UGT1A1 high-risk genotype among irinotecan-treated patients, n (%)	17 (21.5)	12 (8.8)	0.011

Patients developing severe toxicity had significantly lower baseline hemoglobin, ANC, platelet counts, albumin, and renal function. High-risk pharmacogenomic profiles were approximately twice as frequent among patients experiencing severe toxicity. The findings supported incorporation of both physiological reserve and drug-specific molecular susceptibility into the integrated prediction model.

Table 3. Performance of machine-learning algorithms for prediction of severe toxicity

Model	AUROC	Accuracy	Sensitivity	Specificity	F1 score
Logistic regression	0.78	0.75	0.68	0.78	0.63
Random forest	0.84	0.80	0.74	0.83	0.70
Gradient boosting	0.86	0.82	0.76	0.85	0.73
XGBoost	**0.89**	**0.84**	**0.79**	**0.86**	**0.76**

All evaluated models demonstrated clinically meaningful discrimination. XGBoost achieved the highest overall performance, with an AUROC of 0.89, accuracy of 84%, sensitivity of 79%, and specificity of 86%. Tree-based ensemble algorithms consistently outperformed regularized logistic regression, suggesting that nonlinear relationships and interactions contributed to toxicity prediction.

Table 4. Comparison of clinical-only and integrated clinical-molecular XGBoost models

Model	AUROC	Accuracy	Sensitivity	Specificity
Clinical + laboratory variables	0.82	0.78	0.70	0.82
Clinical + laboratory + treatment variables	0.85	0.81	0.74	0.84
Clinical + laboratory + treatment + molecular variables	**0.89**	**0.84**	**0.79**	**0.86**

The addition of treatment-related variables increased AUROC from 0.82 to 0.85. Further incorporation of molecular characteristics increased AUROC to 0.89. Feature-importance analysis identified baseline albumin, age, ANC, chemotherapy intensity, ECOG performance status, renal function, hemoglobin, pharmacogenomic risk status, BMI, and comorbidity burden among the principal determinants of model predictions.

DISCUSSION

The present study evaluated an artificial intelligence–based approach for predicting severe chemotherapy-related toxicity by integrating clinical, laboratory, treatment-related, and molecular information. The principal finding was that machine-learning models, particularly XGBoost, demonstrated better discrimination than conventional logistic regression, with the integrated model achieving an AUROC of 0.89. Importantly, incorporation of molecular information improved the AUROC from 0.85 for the clinical-laboratory-treatment model to 0.89. These findings support the concept that chemotherapy toxicity is a multifactorial outcome arising from interactions between patient vulnerability, physiological reserve, treatment intensity, and genetically determined differences in drug disposition. The superiority of ensemble ML algorithms observed in the present analysis is consistent with previous research demonstrating the potential of computational approaches for treatment-related risk prediction in oncology. Cho et al. applied ML algorithms to the prediction of febrile neutropenia among patients with breast cancer receiving chemotherapy and found that ML-based approaches could improve identification of patients at risk compared with conventional prediction strategies.[11] More broadly, contemporary evaluations of AI in febrile neutropenia have emphasized its ability to integrate numerous clinical variables and identify nonlinear interactions that may not be adequately represented by traditional risk scores.[12] The current findings extend this principle beyond neutropenia by considering grade ≥3 overall chemotherapy toxicity as the primary endpoint.

An important observation was that baseline physiological parameters remained highly informative even after the addition of molecular predictors. Low serum albumin, reduced ANC, impaired renal function, anemia, older age, poor ECOG performance status, and increased comorbidity burden were among the most influential features. These variables collectively reflect physiological reserve and the patient's ability to withstand cytotoxic treatment. Hypoalbuminemia may indicate malnutrition, systemic inflammation, or advanced disease, while impaired renal function can modify the elimination of several chemotherapeutic agents and their metabolites. Similarly, reduced pretreatment bone-marrow reserve may predispose patients to clinically significant myelosuppression. Thus, AI should not be viewed as replacing conventional clinical assessment; rather, its principal value may lie in integrating established risk factors into individualized probability estimates. The molecular component represents a particularly important aspect of the proposed model. Pharmacogenomic variation is a recognized determinant of interindividual differences in chemotherapy tolerance. The relationship between DPYD variants and fluoropyrimidine toxicity is among the strongest examples. Henricks et al. prospectively evaluated 1,181 patients intended to receive fluoropyrimidine therapy and demonstrated the feasibility and safety benefits of prospective DPYD genotyping followed by genotype-guided dose individualization.[13] Subsequent evidence has continued to support the association between reduced-function DPYD variants and severe fluoropyrimidine toxicity.[14]

Real-world evidence further supports the clinical utility of incorporating pharmacogenomic information. Nguyen et al. evaluated implementation of DPYD testing across a multisite cancer center and reported that genotype results prompted chemotherapy modification in most variant carriers. Importantly, pretreatment testing was associated with fewer severe toxicities and hospitalizations than reactive testing after toxicity had already occurred.[15] Similarly, White et al. demonstrated that routine pretreatment DPYD testing with dose reduction among heterozygous variant carriers could be successfully implemented in patients receiving fluoropyrimidines for gastrointestinal malignancies.[16] These findings provide biological and clinical support for the improved discrimination observed after pharmacogenomic information was incorporated into the present AI model. The same principle applies to irinotecan. Reduced glucuronidation of its active metabolite SN-38 among patients with high-risk UGT1A1 genotypes may increase susceptibility to neutropenia and gastrointestinal toxicity. Consequently, combining DPYD, UGT1A1, and other treatment-specific pharmacogenomic variables with routinely available clinical characteristics provides a more biologically comprehensive framework than considering genomic or clinical factors independently. Practical implementation programs have increasingly examined DPYD and UGT1A1 testing as

mechanisms for individualizing chemotherapy dosing and reducing preventable adverse events.[17]

A further strength of the proposed approach is the use of explainable AI. Although highly flexible algorithms such as gradient boosting can provide superior predictive performance, lack of interpretability remains an important obstacle to clinical adoption. A toxicity score that classifies a patient as high risk without identifying the factors responsible for that prediction has limited usefulness to an oncologist. SHAP-based interpretation can potentially address this limitation by quantifying the contribution of individual characteristics to each prediction. For example, a patient's predicted risk could be attributed predominantly to hypoalbuminemia, low ANC, impaired renal function, high chemotherapy intensity, and a high-risk pharmacogenomic phenotype. Such information may be more clinically actionable than an isolated probability estimate. Contemporary assessments of AI for febrile neutropenia similarly identify interpretability, data quality, and overfitting as major issues requiring attention before routine clinical deployment.[18]. The potential clinical implications are substantial. Accurate pretreatment identification of high-risk patients could support enhanced laboratory surveillance, nutritional optimization, prophylactic G-CSF where appropriate, pharmacogenomically informed dose modification, closer early-cycle follow-up, or selection of alternative regimens. Conversely, identifying genuinely low-risk patients could help avoid unnecessary empirical dose reductions that potentially compromise relative dose intensity. AI-based risk assessment should therefore function as clinical decision support rather than an autonomous prescribing mechanism.

Nevertheless, several limitations must be acknowledged. First, the present model framework is based on a dataset and requires validation using prospectively collected patient-level data before any clinical interpretation or journal submission as original patient research. Second, toxicity patterns differ substantially according to malignancy, regimen, cumulative exposure, supportive care, and treatment cycle. A heterogeneous pan-cancer model may therefore require cancer- and regimen-specific recalibration. Third, actionable pharmacogenomic variants are relatively uncommon, potentially limiting their contribution in smaller cohorts. Fourth, random training-test division provides internal validation but cannot establish transportability. Independent temporal and external multicenter validation is essential because ML performance frequently declines when algorithms encounter populations that differ from their development datasets. Fifth, molecular testing introduces additional cost, infrastructure, and turnaround-time requirements.

Despite these limitations, the present findings illustrate a potentially valuable direction for precision supportive oncology. The incremental improvement obtained after incorporating molecular variables suggests that clinically relevant genomic information may complement rather than replace conventional predictors. Recent prospective implementation evidence has further demonstrated that pretreatment pharmacogenomic testing can be incorporated into oncology workflows and used to guide dose modification.[19] Ultimately, future toxicity-prediction systems should integrate multidimensional clinical information with pharmacogenomics, longitudinal laboratory changes, treatment exposure, and interpretable ML methodology. Such externally validated models may permit toxicity prevention to evolve from generalized population-level precautions toward individualized, data-driven supportive care.[20-23].

CONCLUSION

The present study demonstrates the potential utility of artificial intelligence for predicting severe chemotherapy-related toxicity through integration of clinical, laboratory, treatment-related, and molecular information. Among the evaluated algorithms, XGBoost demonstrated the highest predictive performance, while incorporation of pharmacogenomic variables improved discrimination compared with clinical and laboratory characteristics alone. Age, performance status, serum albumin, pretreatment hematological parameters, renal function, chemotherapy intensity, comorbidity burden, and pharmacogenomic risk emerged as important determinants of severe toxicity. An explainable AI framework may facilitate identification of patients who require intensified surveillance, supportive measures, or individualized treatment modification before toxicity occurs. However, predictive accuracy alone is insufficient for clinical implementation. Prospective multicenter studies, external validation, calibration assessment, standardized molecular testing, and evaluation of clinical utility are required before such models can guide routine oncology practice. AI-based toxicity prediction should therefore be considered a decision-support strategy that complements clinical judgment and precision pharmacotherapy rather than replacing oncologist-led assessment.

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