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SYSTEMATIC REVIEW

Risk Prediction Models for Chemotherapy-Induced Myelosuppression: A Systematic Review

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Abstract

Aims/Background Chemotherapy-induced myelosuppression (CIM) is associated with increased risks of life-threatening complications, treatment delays, and reduced therapeutic efficacy. However, the predictors contributing to these risks remain unclear. Therefore, this study aimed to systematically review the existing risk prediction models developed for CIM and to evaluate prognostic factors associated with patient outcomes.

Methods We comprehensively searched domestic and international databases for literature on CIM risk prediction models, covering records from database inception to 31 December 2024. Two researchers independently performed literature screening and data extraction. The risk of bias and applicability of included studies were assessed using the Prediction Model Risk of Bias Assessment Tool (PROBAST).

Results A total of 17 risk prediction models developed for CIM were identified. The area under the curve (AUC) of the selected models ranged from 0.708 to 0.95. Among the six models that underwent external validation, AUC values ranged from 0.708 to 0.95. Fifteen models reported discriminative performance metrics (AUC) exceeding 0.70. The included models incorporated between 2 and 16 predictors, with chemotherapy regimen intensity, baseline haematological parameters (platelet count, haemoglobin, and neutrophil count), and age being the most frequently selected variables.

Conclusion Current CIM risk prediction models demonstrate promising predictive performance, with clinically relevant predictors. However, high bias risks necessitate future optimisation through multicenter prospective studies, the integration of dynamic biomarkers, and standardised validation frameworks to enhance the utility of clinical decision-making.

Key words: myelosuppression; chemically induced; antineoplastic agents; adverse effects; risk assessment; prognostic models; systematic review

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Introduction

Chemotherapy-induced myelosuppression (CIM) refers to the suppression of bone marrow hematopoietic function by chemotherapeutic agents, clinically manifested as neutropenia, anaemia, and thrombocytopenia (Lyman et al, 2011). As the most frequent dose-limiting toxicity in cancer treatment, CIM occurs in 60–80% of patients, with its severity strongly associated with the intensity of the chemotherapy regimen and the patient's baseline characteristics (Venäläinen et al, 2022). Severe CIM may lead to life-threatening infections, hemorrhagic complications, or

even mortality. Approximately 20–30% of patients require chemotherapy dose reductions or treatment delays due to myelosuppression, substantially compromising antitumour efficacy and increasing healthcare costs (Aagaard et al, 2018; Hosmer et al, 2011; Li et al, 2024). Early identification of high-risk populations through risk stratification enables tailored therapeutic interventions, which are critical for optimising chemotherapy safety and clinical outcomes (Moons et al, 2019).

Clinically integrated risk prediction models have emerged as essential tools for managing CIM. Current approaches, including logistic regression, machine learning, and other methodologies, aim to quantify individualised risk based on variables such as age, baseline haematological parameters, and chemotherapy protocols (Chen et al, 2021; Matsumoto et al, 2024; Sapkota et al, 2020). However, their clinical translation is limited by three key challenges: (1) a predominant reliance on single-center retrospective datasets with limited sample sizes and selection bias, compromising model generalisability (Aagaard et al, 2020; Zheng et al, 2022), (2) insufficient external validation, where heterogeneity between derivation and validation cohorts undermines predictive performance (Zhou et al, 2023), and (3) inadequate incorporation of dynamic biomarkers (e.g., serial haematological changes during chemotherapy cycles), constraining real-time risk predictive capabilities (Wang et al, 2024). Collectively, these limitations hinder the clinical utility, leaving healthcare providers without robust decision-support systems for precision-guided interventions. This systematic review aims to critically evaluate existing CIM risk prediction models, providing evidence-based guidance for model selection in clinical practice.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al, 2021). The completed PRISMA checklist is provided as **Supplementary Material 1**.

The research question was formulated using the Population, Intervention, Comparator, Outcome, Timing, and Setting (PICOTS) framework: P (Population)—malignant tumour patients receiving chemotherapy; I (Intervention)—CIM risk prediction models; C (Comparator)—not applicable, as no direct comparison with other interventions was performed; O (Outcome)—CIM occurrence; T (Timing)—from initiation of chemotherapy to CIM diagnosis; S (Setting)—all clinical environments.

The inclusion criteria for manuscript selection were as follows: ① Population: Adult cancer patients (age $\geq$18 years) undergoing chemotherapy; ② Focus: Development or validation of CIM risk prediction models, with CIM defined as hematologic toxicity meeting at least one of the following Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria (U.S. Department of Health and Human Services, 2017): Grade 3–4 neutropenia (absolute neutrophil count $<1.0 \times 10^9$/L); Grade 3–4 anaemia (haemoglobin <80 g/L); Grade 3–4 thrombocytopenia (platelet count $<50 \times 10^9$/L); ③ Study design: Cross-sectional, cohort, or case-control studies. The exclusion criteria included: ① Absence of explicit model de-

velopment methodology; ② Models integrating only a single predictor variable; ③ Unavailability of the full-text publications.

Search Strategy

A comprehensive literature search was performed across eight databases: China National Knowledge Infrastructure (CNKI): https://www.cnki.net/; Wanfang database: https://www.wanfangdata.com.cn/; China Biology Medicine (CBM) database: http://www.sinomed.ac.cn/; PubMed: https://pubmed.ncbi.nlm.nih.gov/; Web of Science: https://www.webofscience.com/; Cochrane Library: https://www.cochranelibrary.com/; Embase: https://www.embase.com/; and Cumulative Index to Nursing and Allied Health Literature (CINAHL): https://www.ebsco.com/products/research-databases/cinahl-database.

A comprehensive search strategy was applied, combining Medical Subject Headings (MeSH) with free-text terms, and supplemented by citation tracking to identify additional relevant studies. The search spanned from database inception to 31 December 2024, without language restrictions.

The Chinese search strategy (example for Wanfang database) comprised: ("myelosuppression" OR "antitumour drug toxicity" OR "hematopoietic stem cell impairment" OR "hematopoietic progenitor cell damage" OR "hematopoiesis" OR "neutropenia" OR "leukopenia" OR "chemotherapy-associated thrombocytopenia" OR "haemoglobin depletion" OR "anaemia") AND ("prediction" OR "risk scoring" OR "risk evaluation" OR "modelling") AND ("chemotherapy" OR "antineoplastic agents" OR "induction chemotherapy" OR "neoplasm" OR "cancer" OR "stem cell transplantation").

The English search strategy (exemplified for PubMed) included: ("tumour"[Title/Abstract] OR "cancer"[Title/Abstract] OR "neoplasms"[Title/Abstract] OR "oncology"[Title/Abstract] OR "malignancy"[Title/Abstract]) AND ((((("myelosuppressed"[All Fields] OR "myelosuppression"[All Fields] OR "myelosuppressive"[All Fields]) AND "chemotherapy-induced myelosuppression"[Title/Abstract]) OR (("febrile"[All Fields] OR "fever"[MeSH Terms]) AND "neutropenia"[Title/Abstract]) OR (("chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms]) AND ("induc*"[All Fields] AND ("thrombocytopenia"[MeSH Terms] OR "thrombocytopenias"[All Fields])))) AND ("predictive model"[Title/Abstract] OR "prognostic model"[Title/Abstract] OR "risk prediction"[Title/Abstract] OR "risk assessment"[Title/Abstract] OR "risk score"[Title/Abstract] OR "predictors"[Title/Abstract]).

Literature Screening and Data Extraction

Two independent researchers performed the literature screening and data extraction, followed by cross-verification of the data. Any discrepancies were resolved through consensus discussions. The data extraction form was designed based on critical appraisal criteria and standardised checklists for systematic reviews of prediction models (Riley et al, 2019).

Risk of Bias and Applicability Assessment

Two independent investigators evaluated the quality of the data using the Prediction Model Risk of Bias Assessment Tool (PROBAST) (https://www.probast.org/), a validated approach developed for assessing risk of bias and applicability in prediction model studies (Moons et al, 2019). The tool evaluates four domains for bias risk: participants, predictors, outcome, and analysis, through 20 signalling questions. Each question is assessed using three-level responses ("yes/probably yes", "no/probably no", or "no information"), with overall domain-level judgment categorised as "high", "low", or "unclear" risk of bias. Moreover, applicability assessment focused on three domains (participants, predictors, outcome) using three-tier ratings ("high concern", "low concern", or "unclear"). Final applicability judgments employed a "one-vote veto" principle, where any domain rated "high concern" resulted in overall high applicability risk.

Statistical Analysis

This systematic review followed the PRISMA 2020 guidelines (**Supplementary Material 1**) (Page et al, 2021) and the methodological framework outlined in the Cochrane Handbook. Elements from the Transparent Reporting of multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) assessment tool were incorporated (Collins et al, 2015) to ensure their adherence to the statement. Significant heterogeneity was observed among the included prediction models regarding study populations (e.g., cancer types, sample sizes ranging from 186 to 58,053), candidate variables (ranging from 4 to 46, with inconsistent inclusion of dynamic biomarkers), modelling approaches (e.g., logistic regression, Least Absolute Shrinkage and Selection Operator [LASSO], Poisson regression, generalised estimating equations [GEE], machine learning), and outcome definitions (CIM subtypes, severity thresholds). Given this heterogeneity, a quantitative meta-analysis was deemed inappropriate. Instead, a narrative synthesis was conducted to systematically describe, compare, and critically appraise existing models for predicting CIM.

Key aspects assessed included model design, performance metrics, validation strategies, and clinical applicability. Reference management and literature organisation were conducted using EndNote 21 (Clarivate Analytics, Inc., Philadelphia, PA, USA). The PROBAST (https://www.probast.org/) tool was used to evaluate the risk of bias and methodological quality of the included studies. Results are summarised in both tabular and graphical formats to enhance clarity and accessibility.

Results

Literature Screening Process and Outcomes

A total of 4002 records were initially identified through database searches. After removing 1114 duplicates, 2888 unique records remained. Title and abstract screening identified 92 articles as potentially relevant. After full-text review, 75 studies were excluded due to unavailability of the full text, inclusion of pediatric patients, study populations not exclusively comprising chemotherapy recipients,

models based on a single predictor, absence of predictive model construction, or inappropriate study design. Ultimately, 17 studies met the inclusion criteria (Aagaard et al, 2020; Aagaard et al, 2018; Bozcuk et al, 2015; Hosmer et al, 2011; Chen et al, 2021; López-Pousa et al, 2010; Lyman et al, 2011; Matsumoto et al, 2024; Razzaghdoust et al, 2018; Razzaghdoust et al, 2020; Sapkota et al, 2020; Sugaya et al, 2025; Venäläinen et al, 2022; Wang et al, 2024; Li et al, 2024; Zheng et al, 2022; Zhou et al, 2023). A flow chart of study design and literature screening is illustrated in Fig. 1.

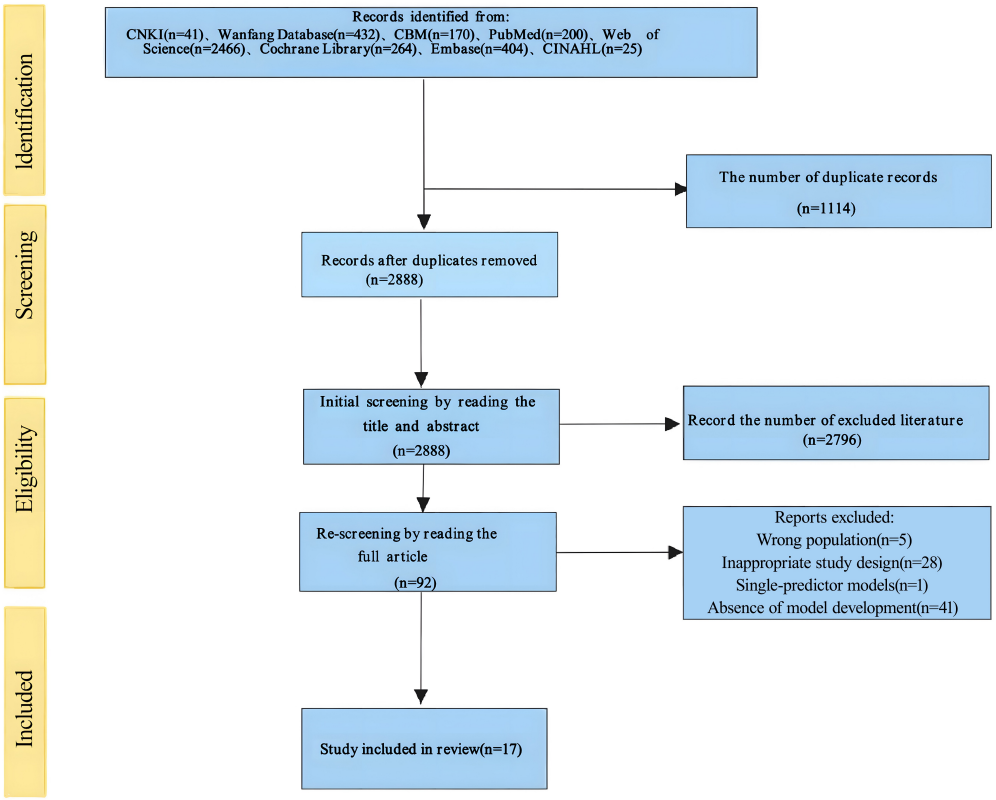

Fig. 1. A flow chart of study design and literature screening. CNKI, China National Knowledge Infrastructure; CBM, China Biology Medicine; CINAHL, Cumulative Index to Nursing and Allied Health Literature.

Characteristics of Included Studies

The 17 included studies reported the development of 17 distinct CIM risk prediction models, with observed CIM incidence ranging from 1.5% to 73.4%. Key study descriptors, including country, study design and phase, cancer population, data source, sample size, and the incidence of chemotherapy-induced myelosuppression (CIM), are systematically summarised in Table 1.

Model Development Overview

The 17 models incorporated 4–46 candidate predictors, with sample sizes ranging from 186 to 58,053 and outcome events between 46 and 2256. Model develop-

Table 1. Baseline characteristics of included studies (n = 17).

Study	Country	Study design	Phase	Population	Data source	Sample size (cases)	CIM incidence (%)
Lyman et al, 2011	United States	Prospective cohort	Development and validation	Solid tumours or malignant lymphoma	115 US clinical sites	2500	20.00
Venäläinen et al, 2022	Finland	Prospective cohort	Development and validation	Non-hematologic malignancies	Electronic records (Turku/Tampere University Hospitals)	5879	4.00
Li et al, 2024	China	Prospective cohort	Development and validation	Breast cancer	Tertiary hospital records (Shiyan)	270	70.37
Hosmer et al, 2011	United States	Prospective cohort	Development and validation	Breast/lung/colorectal/prostate cancer	SEER-Medicare database (US)	58,053	3.90
Aagaard et al, 2018	Denmark	Prospective cohort	Development and validation	Solid tumours or DLBCL	Rigshospitalet (Copenhagen)	6294	5.70
Sapkota et al, 2020	Nepal	Cross-sectional	Development and validation	Chemotherapy-treated cancer patients	Hospital records (Bhaktapur Cancer Hospital)	203	73.40
Chen et al, 2021	China	Retrospective cohort	Development and validation	Geriatric lung cancer patients	Respiratory department records (Zhenjiang Tertiary Hospital)	228	32.89
Matsumoto et al, 2024	Japan	Retrospective cohort	Development and validation	Urothelial cancer receiving GC therapy	Fujita Health University Hospital	186	25.00
Zheng et al, 2022	China	Retrospective cohort	Development and validation	Esophageal cancer	Union Hospital (Huazhong University)	1012	46.70
Aagaard et al, 2020	Denmark	Multicenter retrospective cohort	Development and validation	Chemotherapy-treated solid tumours	Danish National Electronic Health Records and Patient Registry	4590	2.10
Zhou et al, 2023	China	Multicenter retrospective cohort	Development and validation	Eastern Chinese solid tumour patients	EMR databases from three eastern provinces	850	32.50
Wang et al, 2024	China	Retrospective cohort	Development and validation	Cervical cancer	Fujian Cancer Hospital records	394	54.80
Razzaghdoust et al, 2018	Iran	Prospective cohort	Development and validation	Solid tumours/lymphoma	Shahid Beheshti University of Medical Sciences (Shohada-e-Tajrish)	259	21.60
Bozcuk et al, 2015	Turkey	Prospective multicenter	Development and validation	Lung/breast/colorectal cancer	Four Turkish academic hospitals	1089	1.50
López-Pousa et al, 2010	Spain	Multicenter prospective cohort	Development and validation	First-line chemotherapy recipients	Clinical data from 88 Spanish oncology centers	1194	10.00
Razzaghdoust et al, 2020	Iran	Prospective cohort	Development and validation	Solid tumours/lymphoma	Shohada-e-Tajrish Medical Center	305	15.73
Sugaya et al, 2025	Japan	Single-center retrospective cohort	Development and validation	Esophageal cancer (5-FU/CDDP regimen)	Chiba University Hospital EMR	366	28.00

Abbreviations: CIM, chemotherapy-induced myelosuppression; DLBCL, Diffuse Large B-Cell Lymphoma; SEER, Surveillance, Epidemiology, and End Results; 5-FU/CDDP, 5-Fluorouracil /Cis-Dichloro-Diamine Platinum; EMR, Electronic Medical Record; GC, gemcitabine and cisplatin.

Table 2. Characteristics of CIM risk prediction models (n = 17).

Study	Modelling method	Candidate variables	Variable selection	Outcome events	Events per predictor	Model presentation	Missing data handling
Lyman et al, 2011	Multivariable logistic regression	29	Forward stepwise selection	472	16.27	Risk score formula	Multiple imputation
Venäläinen et al, 2022	LASSO regression	30	LASSO regularization	262	8.73	LASSO regression model	NR
Li et al, 2024	Logistic regression	16	Chi-square test with multivariate logistic regression	190	11.88	Nomogram	NR
Hosmer et al, 2011	Multivariable logistic regression	10	Bidirectional stepwise regression	2256	225.60	Points-based system	NR
Aagaard et al, 2018	Poisson regression	20	Univariate screening followed by multivariate model refinement	360	18.00	Risk score	NR
Sapkota et al, 2020	Multivariable logistic regression	4	Statistical significance threshold	149	37.25	Risk stratification framework	Case deletion
Chen et al, 2021	Logistic regression	14	Chi-square test with multivariate logistic regression	75	5.36	Regression equation	NR
Matsumoto et al, 2024	Machine learning	10	Multivariable risk factor analysis	46	4.60	Nomogram	Multiple imputation
Zheng et al, 2022	Machine learning	46	Univariate screening with bidirectional stepwise regression	473	10.30	Nomogram	Multiple imputation
Aagaard et al, 2020	Poisson regression	NR	Univariate screening ($p < 0.1$) with multivariate stepwise selection	326	NR	Scoring system + web tool	Multiple imputation
Zhou et al, 2023	Random forest	22	LASSO with cross-validation + multivariate analysis	276	12.55	Nomogram + online calculator	Multiple imputation
Wang et al, 2024	LASSO-logistic hybrid	18	LASSO-cross-validation + multivariate logistic regression	216	12.00	Nomogram	NR
Razzaghdoust et al, 2018	Multivariable logistic regression	14	Bootstrap-derived coefficient simplification	56	4.00	Simplified scoring system	Multiple imputation
Bozcuk et al, 2015	Generalised estimating equations (GEE)	36	Univariate screening with multivariate GEE modelling	59	1.64	Nomogram	NR
López-Pousa et al, 2010	Multivariate logistic regression	NR	Univariate screening ($p < 0.1$) + stepwise regression	116	NR	Regression equation + scoring	NR
Razzaghdoust et al, 2020	Multivariate logistic regression	14	Univariate screening + backward elimination	48	3.43	Regression equation	NR
Sugaya et al, 2025	GLMM-LASSO	36	Univariate-to-multivariate GLMM-LASSO approach	59	1.64	Nomogram	NR

Abbreviations: LASSO, Least Absolute Shrinkage and Selection Operator; NR, Not Reported; GLMM, Generalised Linear Mixed Model.

Table 3. Predictors, performance metrics, and validation status of CIM risk prediction models (n = 17).

Study	Predictors	Performance metrics	Validation method
Lyman et al, 2011	Five predictors: prior chemotherapy, hepatic/renal dysfunction, leukocyte count, chemotherapy regimen, planned dose intensity	AUC = 0.83 Sensitivity = 90% Specificity = 59% Calibration: NR	Internal validation
Venäläinen et al, 2022	Six predictors: granulocyte colony-stimulating factor (G-CSF) administration, cancer type, pretreatment neutrophil and platelet counts, intravenous chemotherapy regimen, planned dose intensity	AUC = 0.84 Sensitivity: NR Specificity: NR Calibration: NR	Internal validation
Li et al, 2024	Four predictors: surgical history, pre-chemotherapy leukocyte count, haemoglobin level, platelet level	AUC = 0.767 Sensitivity = 0.640 Specificity = 0.812 Calibration: Calibration curve	External validation
Hosmer et al, 2011	Five predictors: cancer type, tumour stage, comorbidity burden, chemotherapy duration, myelosuppressive chemotherapy use	AUC = 0.75 Sensitivity = 24% Specificity = 93% Calibration: NR	External validation
Aagaard et al, 2018	Nine predictors: female, age >65 years, cancer type, disease stage, hypoalbuminemia, hyperbilirubinemia, reduced GFR, pre-chemotherapy infection, chemotherapy class	AUC = 0.80 Sensitivity: NR Specificity: NR Calibration: NR	Internal validation
Sapkota et al, 2020	Two predictors: grade 4 neutropenia, smoking status	AUC: NR Sensitivity = 66.5% Specificity = 94% Calibration: NR	Internal validation

Table 3. Continued.

Study	Predictors	Performance metrics	Validation method
Chen et al, 2021	Four predictors: platinum-based chemotherapy regimen, concomitant adverse reactions, pre-chemotherapy hypoalbuminemia, prechemotherapy decreased haemoglobin	AUC = 0.823 Sensitivity = 81.3% Specificity = 70.5% Calibration: H-L fitting Superiority check	External validation
Matsumoto et al, 2024	Four predictors: platelet count, haemoglobin level, lymphocyte count, gemcitabine dose	AUC = 0.76 Sensitivity = 0.652 Specificity = 0.757 Calibration: NR	Internal validation (cross-validation)
Zheng et al, 2022	Sixteen predictors: chemotherapy regimen, age, sex, platelet (PLT), haemoglobin, blood urea nitrogen (BUN), serum creatinine (Cr), proteinuria, creatine kinase (CK), red blood cell (RBC) count, chemotherapy cycles, antiemetics, hepatoprotective agents, analgesics, vitamin B12, hematologic agents	AUC = 0.883 Sensitivity = 77.8% Specificity = 81.8% Calibration: consistency evaluation	Internal validation (bootstrap)
Aagaard et al, 2020	Six predictors: high-risk FENCE score at baseline, platinum/taxane-based chemotherapy, concurrent radiotherapy, chemotherapy cycle (highest risk in cycle 2), history of febrile neutropenia (FN) or neutropenia, no prophylactic granulocyte colony-stimulating factor (G-CSF)	AUC = 0.78 Sensitivity: NR Specificity: NR Calibration: H-L test	Internal validation
Zhou et al, 2023	Four predictors: age $\geq$65 years, platinum-based chemotherapy, baseline platelet count $<150 \times 10^9$/L, liver dysfunction (ALT >40 U/L)	AUC = 0.845 Sensitivity = 78.6% Specificity = 88.2% Calibration: H-L test	Internal validation (bootstrap) External validation (separate queue)

Table 3. Continued.

Study	Predictors	Performance metrics	Validation method
Wang et al, 2024	Five predictors: age ≥50 years, pre-chemotherapy nutritional risk, prior radiotherapy, bone metastasis, number of chemotherapy cycles	AUC = 0.708 Sensitivity: NR Specificity: NR Calibration: H-L fitting Superiority check	Internal validation (bootstrap) External validation
Razzaghdoust et al, 2018	Six predictors: high-risk regimen without G-CSF, intermediate-risk regimen without G-CSF, age >65 years + elevated ferritin, BMI <23 kg/m^2 + body surface area <2 m^2, eGFR <60 mL/min/1.73 m^2, elevated C-reactive protein	AUC = 0.832 Sensitivity = 82.1% Specificity = 84.2% Calibration: H-L test	Internal validation (50% off cross-validation)
Bozcuk et al, 2015	Five predictors: history of febrile neutropenia, pre-chemotherapy lymphocyte count, cancer type, current chemotherapy cycle, age	AUC = 0.95 Sensitivity = 76% Specificity = 98% Calibration: NR	External validation
López-Pousa et al, 2010	Four predictors: ECOG performance status ≥2, low baseline lymphocytes (OR = 0.67), low baseline neutrophils (OR = 0.90), sex-treatment intent interaction	AUC: NR Sensitivity = 63% Specificity = 67% Calibration: NR	Internal validation
Razzaghdoust et al, 2020	Three predictors: hyperferritinemia (>200/300 ng/mL female/male), eGFR <60 mL/min/1.73 m^2, BMI <23 kg/m^2	AUC = 0.735 Sensitivity = 75% Specificity = 65.4%	Internal validation (bootstrap)
Sugaya et al, 2025	Six predictors: cisplatin dose, 5-Fluorouracil dose, leucovorin use, sex, cholinesterase level, platelet count	AUC = 0.781 Calibration: NR	Internal validation

Abbreviations: GFR, Glomerular Filtration Rate; AUC, area under the curve; H-L, Hosmer-Lemeshow; eGFR, estimated Glomerular Filtration Rate; ECOG, Eastern Cooperative Oncology Group; OR, Odds Ratio; ALT, Alanine Aminotransferase; FENCE, Febrile Neutropenia after Chemotherapy; BMI, Body Mass Index.

Table 4. Model performance stratified by CIM subtypes.

CIM subtype	Number of studies	Mean AUC (range)	Common predictors (frequency)
Neutropenia	12	0.82 (0.67–0.95)	Chemotherapy regimen (100%), baseline neutrophil count (92%), age (85%)
Thrombocytopenia	5	0.75 (0.70–0.88)	Baseline platelet count (100%), liver/kidney function (80%), chemotherapy cycles (60%)
Anaemia	3	0.71 (0.68–0.77)	Baseline haemoglobin (100%), iron metabolism markers (67%), tumour stage (67%)

ment strategies included logistic regression (8 studies), LASSO regression (3 studies; Sugaya et al, 2025; Venäläinen et al, 2022; Wang et al, 2024), Poisson regression (2 studies; Aagaard et al, 2020; Aagaard et al, 2018), generalised estimating equations (1 study; Bozcuk et al, 2015), and machine learning algorithms (3 studies; Matsumoto et al, 2024; Zheng et al, 2022; Zhou et al, 2023). Detailed characteristics of model development are presented in Table 2.

Model Performance and Predictors

The 17 included models incorporated 2–16 predictors, with age, chemotherapy regimen, and baseline haematological parameters being the most frequently identified predictors. Comprehensive details regarding predictor composition, model performance metrics, and validation status are systematically presented in Table 3.

Stratified Analysis by CIM Subtypes

The predictive performance of the models varied significantly across CIM subtypes. Models targeting neutropenia generally demonstrated the highest accuracy (mean area under the curve [AUC] = 0.82), followed by models for thrombocytopenia (mean AUC = 0.75), while anaemia models showed relatively lower performance (mean AUC = 0.71) (Table 4).

Distinct Predictors Dominated Different Subtypes

Neutropenia models consistently incorporate chemotherapy regimen toxicity (100% of studies) and baseline neutrophil count (92%), reflecting the link between cytotoxic drug intensity, pre-treatment hematopoietic reserves, and risk of myelosuppression. Thrombocytopenia models commonly emphasised liver/kidney function parameters (e.g., creatinine, Alanine Aminotransferase [ALT]; 80%) and chemotherapy cycle duration (60%), underscoring the role of metabolic clearance capability and cumulative drug exposure. Anaemia models frequently incorporated baseline haemoglobin levels (100%), along with iron metabolism markers (67%) and tumour stage (67%), suggesting interactions among chronic inflammation, disrupted iron homeostasis, and disease progression (Table 4).

Risk of Bias and Applicability Assessment

The PROBAST assessment revealed significant methodological concerns across the included studies. All 17 studies were judged to have a high overall risk of bias,

Table 5. Risk of bias and applicability assessments of included models.

Study	Risk of bias				Applicability			Overall judgment	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	Risk of bias	Applicability
Lyman et al, 2011	Low	Low	Low	High	Low	Low	Low	High	Low
Venäläinen et al, 2022	Low	Low	Low	High	Low	Low	Low	High	Low
Li et al, 2024	Low	High	Low	High	Low	Low	Low	High	Low
Hosmer et al, 2011	Low	Low	Low	High	Low	Low	Low	High	Low
Aagaard et al, 2018	Low	Low	Low	High	Low	Low	Low	High	Low
Sapkota et al, 2020	High	High	Low	High	Low	High	Low	High	High
Chen et al, 2021	High	High	Low	High	High	Low	Low	High	High
Matsumoto et al, 2024	High	High	Low	High	Low	Low	Low	High	Low
Zheng et al, 2022	High	High	Low	High	Low	Low	Low	High	Low
Aagaard et al, 2020	Low	Low	Low	High	Low	Low	Low	High	Low
Zhou et al, 2023	Low	Low	Low	High	Low	Low	Low	High	Low
Wang et al, 2024	High	High	Low	High	Low	High	Low	High	High
Razzaghdoust et al, 2018	High	Low	Low	High	Low	Low	Low	High	Low
Bozcuk et al, 2015	Low	Low	Low	High	Low	Low	Low	High	Low
López-Pousa et al, 2010	Low	High	Low	High	Low	Low	Low	High	Low
Razzaghdoust et al, 2020	High	Low	Low	High	Low	Low	Low	High	Low
Sugaya et al, 2025	High	Low	Low	High	Low	Low	Low	High	Low

primarily driven by flaws in the 'Analysis' domain (Table 5). Detailed evaluations categorised these methodological limitations into four domains.

Bias Related to the Study Population

Five studies (Chen et al, 2021; Matsumoto et al, 2024; Wang et al, 2024; Zheng et al, 2022; Sugaya et al, 2025) were based on single-center retrospective cohorts, raising concerns regarding selection bias and limited generalisability.

Bias Related to Predictors

Seven studies (Chen et al, 2021; Matsumoto et al, 2024; Razzaghdoust et al, 2018; Sapkota et al, 2020; Wang et al, 2024; Li et al, 2024; Zheng et al, 2022) did not incorporate dynamic biomarkers, such as serial neutrophil counts or platelet trends, thereby limiting clinical applicability.

Bias Related to Analyses

Missing Data Handling

Ten studies (Aagaard et al, 2018; Bozcuk et al, 2015; Hosmer et al, 2011; Chen et al, 2021; López-Pousa et al, 2010; Matsumoto et al, 2024; Razzaghdoust et al, 2018; Sapkota et al, 2020; Wang et al, 2024; Zheng et al, 2022) either excluded cases with missing data or did not report their handling strategies, thereby introducing a potential risk of selection bias. In contrast, six studies (Lyman et al, 2011; Matsumoto et al, 2024; Zheng et al, 2022; Aagaard et al, 2020; Zhou et al, 2023; Razzaghdoust et al, 2018) employed multiple imputation, which is generally considered a more robust approach.

Categorisation of Continuous Variables

Six studies (Hosmer et al, 2011; Chen et al, 2021; Razzaghdoust et al, 2018; Sapkota et al, 2020; Wang et al, 2024; Zheng et al, 2022) dichotomised continuous predictors, such as age and haematological parameters, into categorical variables. This approach can reduce statistical power and mask potential non-linear correlation or dose-response relationships.

External Validation

Out of the total included studies, only 6 performed external validation (Chen et al, 2021; Li et al, 2024; Hosmer et al, 2011; Wang et al, 2024; Bozcuk et al, 2015; Zhou et al, 2023).

Evaluation of Applicability

The applicability of the included CIM risk prediction models was systematically evaluated across three domains: representativeness of the study population, consistency of predictor measurement, and clinical relevance of outcomes. Overall, the generalisability of the included models is supported by their applicability in the final studies. These models demonstrate good applicability and do not present significant issues with generalisability, as indicated in Table 5.

Participant Representativeness

Six studies (Chen et al, 2021; López-Pousa et al, 2010; Razzaghdoust et al, 2018; Sapkota et al, 2020; Wang et al, 2024; Zheng et al, 2022) applied restrictive inclusion criteria, excluding high-risk subgroups such as elderly patients (≥80 years), patients with advanced renal or hepatic impairment, and individuals with prior hematopoietic stem cell transplantation. For instance, Chen et al (2021) excluded patients with a baseline Eastern Cooperative Oncology Group (ECOG) performance status >2, despite evidence indicating that functional decline exacerbates CIM susceptibility (Lyman et al, 2011). Such exclusions compromise the applicability of these models to real-world oncology populations, where complex comorbidities are common.

Predictor Measurement

Five studies (Bozcuk et al, 2015; Chen et al, 2021; López-Pousa et al, 2010; Razzaghdoust et al, 2018; Sapkota et al, 2020) did not standardise the timing or methodology for assessing baseline haematological parameters. In these studies, baseline neutrophil counts were measured at variable intervals—ranging from 24 hours to 14 days before chemotherapy—potentially inflating inter-study heterogeneity. Additionally, two models (Sugaya et al, 2025; Zheng et al, 2022) incorporated non-routine biomarkers (e.g., creatine kinase, cholinesterase), which may limit their feasibility in resource-constrained clinical settings.

Outcome Alignment

While all included studies appropriately defined severe CIM (Grade 3–4 neutropenia, anaemia, or thrombocytopenia) as the primary outcome, five models (Chen et al, 2021; López-Pousa et al, 2010; Razzaghdoust et al, 2018; Sapkota et al, 2020; Wang et al, 2024) did not account for competing risks such as early treatment discontinuation, non-CIM-related death, or hospitalisation for unrelated complications. Failure to address these factors may lead to an overestimation of CIM risk.

Analysis of Included Models, Model Performance and Methodological Comparisons

A cross-comparison of the 17 included studies revealed distinct performance patterns across modelling approaches. Machine learning models (Matsumoto et al, 2024; Zheng et al, 2022; Zhou et al, 2023) demonstrated strong discriminative performance (AUC: 0.76–0.883), although their performance was not consistently superior to that of traditional regression approaches. For instance, the random forest model by Zhou et al (2023) achieved an AUC of 0.845 with satisfactory calibration (Hosmer-Lemeshow test, $p = 0.230$) (Zhou et al, 2023), whereas the GEE-based model reported an even higher AUC of 0.95 (Bozcuk et al, 2015). However, the clinical interpretability of machine learning models was limited, as only one study (Matsumoto et al, 2024) incorporated visualisation tools (e.g., nomograms), compared to 64% (9/14) of regression-based models.

Predictor Heterogeneity and Key Clinical Variables

Substantial heterogeneity in predictor selection was observed across studies, with models incorporating between 4 and 46 variables. Commonly included predictors were baseline haematological parameters, such as platelet count, haemoglobin, or neutrophil count (10/17, 59%), chemotherapy regimen intensity (11/17, 65%), and age (6/17, 35%).

Validation Strategies and Generalisability

Only 35% of the studies (6/17) performed external validation. Models developed from multicenter datasets usually demonstrate superior generalisability, with minimal AUC decline between internal and external validation ($\Delta AUC < 0.03$). For example, the model by Lyman et al (2011) maintained an AUC of 0.83 in external validation. In contrast, single-center models, such as the one developed by Chen et al (2021), exhibited significant performance degradation upon external validation ($\Delta AUC = 0.091$, declining from 0.823 to 0.732), highlighting the increased risk of overfitting in models derived from a small sample size (n = 228).

Calibration Methodologies and Reporting Gaps

Calibration practices varied considerably across the included studies. Among the 17 included models, only one (Li et al, 2024) explicitly reported using a calibration curve. Most other models assessed calibration using statistical tests such as the Hosmer-Lemeshow test or did not report calibration methods at all (8/17). Four studies (Zheng et al, 2022; Wang et al, 2024; Zhou et al, 2023; Razzaghdoust et al, 2020) employed bootstrap resampling for calibration refinement.

Discussion

Predictive Performance, Methodological Limitations, and Core Risk Factors

Current risk prediction models for chemotherapy-induced myelosuppression (CIM) demonstrate moderate to high discriminative performance, with reported AUC values ranging from 0.708 to 0.95, highlighting their potential clinical utility. However, this systematic review indicates that their real-world applicability is substantially limited by methodological shortcomings and insufficient validation. Most models were developed using retrospective or single-center datasets (11/17), with inadequate handling of missing data (10/17) and the inappropriate dichotomisation of continuous variables (6/17), leading to a high overall risk of bias. The consequences were particularly evident during external validation, which was reported in only 6 of the 17 included models, where performance often declined, with AUC reductions ranging from 0.09 to 0.18 compared to internal validation. In contrast, models developed using multicenter or prospective datasets consistently achieved more robust and generalisable outcomes (AUC: 0.83–0.84), reinforcing the importance of rigorous design, representative sampling, and transparent reporting in developing clinically applicable prediction tools.

A key finding from our review is the recurrent use of a core set of predictors across the 17 included models, providing a foundation for standardised clinical

risk stratification. The most consistently incorporated variables were chemotherapy regimen intensity (65%), baseline hematologic parameters—particularly neutrophil count (59%)—and patient age (35%) (Lee and Lockwood, 2013). These predictors reflect well-established pathophysiological mechanisms underlying CIM, reinforcing their strong clinical relevance.

Advanced age, particularly beyond 65 years, consistently emerged as a significant risk factor for CIM. This increased vulnerability among older adults is likely multifactorial. Age-related declines in hematopoietic stem cell (HSC) reserves reduce the bone marrow's regenerative capacity following cytotoxic injury, a process mediated by telomere shortening (Su et al, 2024) and adverse remodelling of the bone marrow microenvironment (Lee et al, 2019). Additionally, age-associated reductions in renal clearance can prolong systemic exposure to chemotherapeutic agents, thereby intensifying therapy-related toxicity (Kao et al, 2025).

The intensity chemotherapy regimen was found to be another dominant predictor of CIM risk. High-intensity regimens—particularly those including anthracyclines or platinum-based compounds—cause profound myelosuppression by directly targeting proliferating bone marrow progenitors and damaging stromal support cells. Mechanistically, these agents induce DNA strand breaks and generate reactive oxygen species (Collins et al, 2015), thereby disrupting hematopoiesis at multiple levels (Crawford et al, 2024; Richardson et al, 2015).

Lastly, a low baseline neutrophil count was observed as a strong independent predictor of subsequent CIM, reflecting an already compromised granulopoietic reserve at the start of treatment. This feature predisposes patients to delayed hematologic recovery and increases the risk of prolonged or severe myelosuppression (Wang et al, 2006).

Subgroup Performance and Pathophysiological Considerations

Stratified analyses revealed notable variability in model performance across hematologic toxicity subtypes, offering valuable insights into the predictive landscape of CIM. Models predicting neutropenia demonstrated the highest discriminative ability, with a mean AUC exceeding 0.80, followed by thrombocytopenia models (mean AUC = 0.75), while those predicting anaemia showed comparatively lower performance (mean AUC = 0.71).

This gradient in predictive performance likely reflects basic differences in the pathophysiology of each hematologic complication. Neutropenia is closely linked to chemotherapy intensity and the inherently rapid turnover of granulocytes, rendering it more predictable using treatment-related variables (Richardson et al, 2015). Conversely, thrombocytopenia is more dependent on individual pharmacokinetics—such as hepatic and renal clearance capacity—and cumulative chemotherapy exposure (Kintzel, 2001). Anaemia presents the greatest predictive challenge owing to its multifactorial aetiology, which involves not only baseline haemoglobin levels but also dysregulated iron metabolism, chronic inflammation, and tumour-related factors (Crawford et al, 2024). These findings underscore the need for toxicity-specific modelling strategies that account for distinct biological mechanisms to improve predictive accuracy.

Performance and Limitations of Machine Learning Models

Despite their promising predictive performance, a major limitation of current machine learning (ML) applications in CIM prediction is poor interpretability. Although all three ML studies incorporated clinician-friendly visualisation tools (e.g., nomograms), similar to the 64% of regression-based models that provided interpretable formats, the inherently 'black-box' nature of ML algorithms continues to impede intuitive clinical understanding. This lack of transparency remains a significant barrier to clinician trust and the widespread adoption in practice.

While ML methods are theoretically well-equipped to capture complex, time-dependent clinical patterns, their application in CIM risk prediction remains limited. Of the three ML-based models included in this review (Matsumoto et al, 2024; Zheng et al, 2022; Zhou et al, 2023), none incorporated high-frequency dynamic biomarkers, such as serial haematological measurements during chemotherapy. Across all 17 models reviewed, only five (Zheng et al, 2022; Wang et al, 2024; Bozcuk et al, 2015; Aagaard et al, 2020; Razzaghdoust et al, 2018)—regardless of modelling approach—incorporated time-varying predictors, and these were simplified predictors such as chemotherapy cycle number or dose modifications. Moreover, the highest reported AUC among these studies was 0.95 (Bozcuk et al, 2015). However, these variables did not reflect fine-grained physiological trends. Future research should prioritise integrating granular longitudinal biomarkers while ensuring model interpretability to support clinical implementation.

To address these limitations and facilitate clinical translation, future research should prioritise several key directions. First, developing and validating models in large, multicenter cohorts—including underrepresented populations such as elderly patients ($\geq$80 years) and individuals with comorbidities like renal impairment—is essential for improving generalisability and ensuring equitable care. For nursing care, broadly applicable models enable individualised risk assessment and guide targeted interventions across diverse clinical settings. Second, integrating dynamic biomarkers, such as serial neutrophil counts, through electronic health records (EHRs) offers an opportunity for real-time, cycle-specific risk prediction. Embedding such models within EHR systems could trigger automated alerts at critical time points (e.g., pre-chemotherapy, nadir periods), allowing nurses to initiate proactive monitoring, provide patient education on infection prevention, and coordinate timely interventions such as growth factor support. Given their frontline role, nurses are uniquely positioned to ensure accurate data collection and to act promptly on predictive insights.

Third, implementing explainable artificial intelligence (XAI) approaches, such as SHapley Additive exPlanations (SHAP), can improve interpretability by elucidating the contribution of individual predictors to risk estimates. This transparency enhances nurses' ability to communicate personalised risk information to patients, support shared decision-making, and advocate for appropriate care based on the model's underlying rationale.

Finally, adherence to methodological standards, such as the TRIPOD guidelines and external validation using independent cohorts, remains critical to ensure model transparency, reproducibility, and clinical readiness. Nurses play a central

role in evaluating, implementing, and integrating validated tools into clinical workflows. Embedding risk scores within nursing assessments and EHR-based decision support systems can promote standardised care and evidence-based practice. Furthermore, nurses can lead quality improvement and research initiatives to refine prediction models by incorporating nursing-sensitive data (e.g., patient-reported outcomes, functional status) and evaluating the impact of model implementation on clinical outcomes, such as febrile neutropenia rates, unplanned hospitalisations, and resource utilisation.

This study has several limitations that should be acknowledged. Potential publication bias may have been introduced by excluding grey literature. Models developed using small sample sizes may have limited statistical power, while machine learning approaches (e.g., random forest) usually experience poor interpretability and lack validation against clinical outcomes. Moreover, due to the substantial heterogeneity among the predictive models included, this review relied solely on descriptive analysis rather than conducting a meta-analysis.

Conclusion

Current CIM risk prediction models show promising performance but remain in the early stage of development, with limitations due to bias and inadequate clinical integration. The lack of external or multicenter validation in most models limits their generalisability. Future studies should incorporate dynamic predictors, embed models into electronic health records, and apply explainable AI to enhance transparency. Adherence to PROBAST and TRIPOD reporting guidelines will be essential to reducing bias and supporting clinical adoption.

Key Points

- Most CIM risk prediction models show moderate-to-high discrimination but experience high bias due to retrospective design and poor management of missing data.
- Age, chemotherapy regimen intensity, and baseline neutrophil count are the most commonly used predictors.
- Dynamic haematological indicators are rarely incorporated, limiting real-time clinical utility.
- Future research should enhance generalisability by incorporating multicenter validation and adopting explainable machine learning approaches.

Availability of Data and Materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

JH and HY conceptualised and designed the study. JH and HY drafted the initial manuscript. NL and FL contributed to data collection, literature screening, and analysis. All authors critically revised the manuscript for important intellectual content and approved the final version. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2025.0452.

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