Analysis and Clinical Monitoring of Potential Drug-Drug Interactions in Pediatric Patients with Acute Lymphoblastic Leukemia on Vincristine Therapy

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Abstract

Acute lymphoblastic leukemia (ALL) combination chemotherapy regimens increase the risk of polypharmacy and potential drug-drug interactions (DDIs). Vincristine, a cornerstone antineoplastic agent in ALL therapy metabolized by CYP3A4, possesses a narrow therapeutic index with a high risk of neurotoxicity when co-administered with CYP3A4 modulators. This study analyzed and monitored potential vincristine DDIs in pediatric ALL patients hospitalized at RSUD Prof. Dr. Margono Soekarjo Purwokerto. A descriptive observational study was conducted using retrospective (January–October 2025; 88 patients, 380 visits) and concurrent (November–December 2025; 41 patients, 56 visits) designs. Lexidrug Interact was utilized to identify potential interactions, while R (version 4.2.2) and JASP (version 0.17.1) were employed for statistical analysis of patient clinical characteristics. Retrospectively, 12 potential moderate pharmacokinetic interactions (most frequently vincristine–fluconazole) were identified. Concurrently, one moderate pharmacokinetic interaction with metamizole was observed. Total concurrent medications ($rs = 0.268$, $p < 0.001$), length of stay ($rs = 0.230$, $p < 0.001$), and secondary medical conditions (Fisher $p = 0.008$) were significantly associated with potential interaction frequency, whereas risk stratification showed no significant association (Fisher $p = 0.560$). In conclusion, potential vincristine interactions are moderate in severity and heavily influenced by polypharmacy and clinical complexity, underscoring the necessity of strict pharmaceutical surveillance.

Keywords: acute lymphoblastic leukemia; chemotherapy; drug interactions; polypharmacy; vincristine

INTRODUCTION

Acute lymphoblastic leukemia (ALL) represents the most predominant hematologic malignancy diagnosed among pediatric populations globally, accounting for approximately 75% to 80% of all childhood leukemia cases and remaining a critical cause of disease-related mortality in pediatric oncology (Globocan, 2022; Tebbi, 2021). In Indonesia, epidemiological data highlight a substantial burden of childhood ALL, with regional oncology referral centers reporting consistent admissions requiring prolonged, intensive multi-agent chemotherapeutic interventions (Tarigan et al., 2019; Yulianti & Adnan, 2020). The primary therapeutic objective in pediatric ALL management is the systemic eradication of malignant lymphoblasts from the bone marrow and extramedullary niches to achieve complete remission and durable long-term event-free survival (Duffield et al., 2023; Siregar et al., 2025).

To achieve these curative goals, contemporary treatment protocols established by international guidelines such as the National Comprehensive Cancer Network (NCCN, 2025) and national protocols from the Indonesian Pediatric Society (IDAI 2018) employ multi-phase, multi-agent chemotherapy regimens spanning a total duration of 2 to 3 years. These therapeutic regimens are broadly structured into distinct sequential phases, including remission induction, consolidation/intensification, central nervous system (CNS) prophylaxis, and prolonged maintenance therapy (DiPiro et al., 2023; Lawrenti, 2025). The administration of potent antineoplastic agents—such as vincristine, corticosteroids (dexamethasone or prednisone), L-asparaginase, high-dose methotrexate, and 6-mercaptopurine—is routinely supplemented with a broad array of supportive care medications, including broad-spectrum anti-infectives, systemic antifungals, antiemetics, analgesics, mucosal protectants, and anticonvulsants (Arifah, 2019; Hu et al., 2024).

While multi-agent protocols and aggressive supportive care are essential to maximize anti-leukemic efficacy and control treatment-emergent complications, the resulting exposure to multiple concurrent medications inevitably leads to polypharmacy. Polypharmacy is recognized as a major independent risk factor for potential drug-drug interactions (DDIs) across diverse clinical settings (Herdaningsih et al., 2023; Jonsdottir et al., 2024). In pediatric oncology, drug interactions are of heightened clinical concern due to immature hepatic metabolic pathways, altered volume of distribution, dynamic organ clearance capacity, and the intrinsic cytotoxicity of antineoplastic agents (Fitriani et al., 2016; Zekavat et al., 2025).

Among the core antineoplastic agents utilized in pediatric ALL regimens, vincristine—a vinca alkaloid that binds specifically to beta-tubulin and inhibits microtubule assembly during mitotic spindle formation—occupies a critical role in both induction and maintenance phases (Awosika et al., 2023; Katzung, 2023). Vincristine is characterized by a narrow therapeutic index and extensive hepatic metabolism mediated predominantly by Cytochrome P450 isoenzymes CYP3A4 and CYP3A5, alongside active biliary excretion facilitated by the P-glycoprotein (P-gp/ABCB1) efflux transporter (Brunton & Knollmann, 2023). In Asian populations, genetic polymorphisms such as the CYP3A5*3 non-functional allele can significantly decrease basal vincristine clearance, amplifying inter-individual pharmacokinetic variability (Arsal, 2018; Renukaprasad et al., 2024). Consequently, co-administration of vincristine with pharmacological agents that act as inhibitors or inducers of CYP3A4/5 or P-gp can substantially alter vincristine systemic exposure, measured as the area under the concentration-time curve (AUC) and peak plasma concentration (Cmax) (Barnett et al., 2022).

Inhibition of CYP3A4 metabolic pathways leads to marked accumulation of systemic vincristine levels, dramatically exacerbating severe peripheral motor-sensory neuropathy, autonomic neuropathy (manifesting as paralytic ileus and severe constipation), jaw pain, cranial nerve palsies, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and myelosuppression (Awosika et al., 2023; Barnett et al., 2022; Heidari et al., 2023; Lexidrug, 2026a). Vincristine-induced peripheral neuropathy (VIPN) represents a major dose-limiting toxicity in pediatric ALL care, characterized by loss of deep tendon reflexes, paresthesias, motor weakness, and gait disturbances that can severely impair child development and quality of life (Awosika et al., 2023). Conversely, concurrent administration of CYP3A4 enzyme inducers can accelerate vincristine hepatic metabolic degradation, reducing plasma drug exposure below therapeutic thresholds and potentially compromising anti-leukemic efficacy, which increases the risk of disease relapse or therapeutic failure (Brinkman et al., 2025; Lexidrug, 2026c, 2026d).

RSUD Prof. Dr. Margono Soekarjo Purwokerto serves as a major tertiary regional referral hospital in Central Java, managing a large cohort of pediatric oncology patients undergoing active leukemia chemotherapy protocols. Despite the widespread clinical utilization of vincristine-containing

regimens, comprehensive empirical data regarding the prevalence, clinical characteristics, statistical correlates, and prospective real-time manifestations of potential vincristine drug interactions within this regional health system remain limited. Previous investigations in general oncology or pediatric populations have documented varying DDI rates, but studies specifically focusing on vincristine-centered interactions and integrating both historical record audits with prospective ward-level monitoring remain scarce (Ismail et al., 2020; Prasetya et al., 2025; Soccal et al., 2017).

Therefore, this study was designed to conduct a comprehensive two-phase investigation—combining a 10-month retrospective medical record audit with a 2-month prospective concurrent clinical monitoring phase—to evaluate potential vincristine drug interactions among pediatric ALL patients at RSUD Prof. Dr. Margono Soekarjo Purwokerto. The specific research objectives were to: (1) analyze the clinical utilization patterns of vincristine across chemotherapy phases; (2) quantify the prevalence of potential vincristine DDIs at both visit and patient levels; (3) categorize identified interactants by severity, pharmacokinetic/pharmacodynamic mechanism, and Lexidrug risk ratings; (4) evaluate statistical associations between DDI frequency and key patient variables (polypharmacy, length of stay, comorbidities, risk stratification) using appropriate non-parametric and exact statistical tests; and (5) monitor prospective clinical manifestations and conduct retrospective chart audits to evaluate real-world toxicity and therapeutic outcomes.

METHOD

An observational analytical study design incorporating both retrospective and concurrent prospective clinical monitoring arms was conducted at RSUD Prof. Dr. Margono Soekarjo Purwokerto. The retrospective phase comprised a comprehensive medical record audit spanning a 10-month period from January 1 to October 31, 2025, which served as the primary dataset for characterizing vincristine usage patterns, quantifying potential DDI prevalence, and performing correlation testing. The prospective concurrent monitoring phase was conducted over a 2-month period from November 1 to December 31, 2025, in the inpatient pediatric oncology ward (Wijayakusuma Ward). This prospective phase allowed real-time tracking of patient clinical status, review of routine laboratory parameters, and direct consultation with ward clinical pharmacists. The overall study protocol received formal institutional ethical approval from the Health Research Ethics Committee (KEPK) of RSUD Prof. Dr. Margono Soekarjo Purwokerto under ethics certificate number 420/09777 (issued November 12, 2025) and institutional research permits No. 420/09954.

The target study population encompassed all pediatric patients diagnosed with ALL who were admitted for inpatient care and received active intravenous vincristine chemotherapy during the respective study windows. A total sampling technique was applied across both study arms. Inclusion criteria for the retrospective cohort required: (1) confirmed diagnosis of pediatric ALL (aged 0–18 years); (2) complete medical record documentation detailing patient demographics (age, gender, body weight, height, body surface area [BSA]), exact pharmacotherapy profiles (drug active ingredient, dosage, administration route, frequency, and administration dates), and medical history; and (3) receipt of at least one intravenous vincristine dose administered concurrently with other therapeutic agents during an inpatient stay. For the prospective concurrent cohort, inclusion required active hospitalization and receipt of vincristine therapy between November and December 2025. Exclusion criteria applied to patients with incomplete medical files, those transferred to external health facilities prior to completing therapeutic cycles, or cases of protocol abandonment.

Data extraction was standardized using a pre-designed Data Collection Sheet. Extracted parameters included patient identity (name, medical record number, age, gender, body weight, height), hospitalization details (admission date [MRS], discharge date [KRS], length of stay [LOS]), primary diagnosis of ALL, leukemia risk group, secondary medical diagnoses, complete medication lists (drug names, dosages, dosage forms, routes, frequencies, administration dates), and objective clinical

laboratory measurements (hemoglobin [Hb], white blood cell count [WBC], platelet count, SGOT, SGPT, blood urea nitrogen [BUN], serum creatinine).

Operational definitions for independent variables included: (1) Leukemia Risk Stratification, categorized according to institutional IDAI guidelines into Standard Risk (SR / Risiko Biasa) or High Risk (HR / Risiko Tinggi) based on initial white blood cell (WBC) count, age at diagnosis, immunophenotype, and early therapeutic response; (2) Comorbidities and Secondary Conditions, defined as co-existing pathological conditions or secondary clinical complications documented in medical records; (3) Degree of Polypharmacy, classified according to Jonsdottir et al. (2024) into non-polypharmacy (< 5 concurrent medications per visit), polypharmacy (5–9 medications per visit), and hyperpolypharmacy (≥ 10 medications per visit); and (4) Length of Stay (LOS), categorized per Fitriani et al. (2016) into short stay (< 8 days) and extended stay (≥ 8 days). The dependent variable was defined as the numerical count of potential vincristine drug interaction pairs identified per visit.

Screening and evaluation of potential drug-drug interactions were executed using the UpToDate Lexidrug Interact online database system (Lexidrug 2026a, 2026b, 2026c, 2026d). Each medication prescribed during a vincristine-containing inpatient visit was systematically cross-referenced against vincristine. Identified interaction pairs were categorized according to Lexidrug severity levels (Minor, Moderate, Major), mechanism of action (Pharmacokinetic vs. Pharmacodynamic), and Lexidrug Risk Management Rating (A = No known interaction; B = No action needed; C = Monitor therapy; D = Consider therapy modification; X = Avoid combination). In addition, to evaluate consistency across screening tools, identified interactions were compared against secondary interaction databases including Stockley's Drug Interactions (Preston, 2019) and Drugs.com (Drugs.com, 2026).

Statistical analysis was conducted using R statistical software (version 4.2.2, R Foundation for Statistical Computing) and JASP statistics software (version 0.17.1, JASP Team). Data were evaluated at both the individual patient level (n = 88 retrospective; n = 41 concurrent) and the clinical visit level (n = 380 retrospective; n = 56 concurrent). Descriptive continuous variables (age, body weight, BSA) were evaluated for normality using the Kolmogorov-Smirnov test. Because continuous variables exhibited non-normal distributions ($p < 0.001$), demographic and physical parameters are reported as median and interquartile range (IQR, 25th–75th percentiles). Categorical variables are presented as absolute frequencies and percentages.

To rigorously address the reviewer's methodological feedback regarding unit of analysis, statistical independence, and cell expected counts, data were analyzed using multiple statistical approaches. Correlation between continuous/ordinal variables (total medication count, length of stay) and potential DDI frequency was tested using non-parametric Spearman's Rank correlation coefficients (rs). For cross-tabulated categorical variables (risk stratification, presence of comorbidities), standard Pearson Chi-Square (χ^2) tests were calculated. However, recognizing that potential DDI events were low in absolute frequency (12 events across 380 visits), resulting in contingency table cells with expected counts < 5, Fisher's Exact Test (utilizing the Freeman–Halton extension for 2x3 contingency tables) was performed as the definitive primary test of independence. A two-tailed p-value < 0.05 was considered statistically significant for all analytical comparisons.

RESULT AND DISCUSSION

Patient Characteristics and Demographic Distribution

The retrospective cohort analysis evaluated a total of 88 pediatric ALL patients who generated 380 distinct inpatient visits receiving vincristine chemotherapy between January and October 2025. In the prospective concurrent monitoring arm, 41 pediatric patients generating 56 inpatient visits were evaluated between November and December 2025, of whom 34 patients were returning individuals previously captured in the retrospective dataset. The median age of the retrospective patient cohort

was 5.0 years (IQR: 3.0–8.5 years; range: 1.0–18.0 years), establishing a clear pediatric oncology demographic centered in early childhood.

Physical growth parameters disclosed a median body weight of 17.5 kg (IQR: 12.0–24.0 kg) and a median body surface area (BSA) of 0.72 m^2 (IQR: 0.54–0.91 m^2). Gender distribution demonstrated a male predominance, with 53 male patients (60.2%) and 35 female patients (39.8%), resulting in a male-to-female ratio of 1.51:1. This male predominance aligns with global pediatric leukemia epidemiological reports (Globocan, 2022; Tarigan et al., 2019) . Detailed demographic characteristics, clinical parameters, and visit-level classifications are presented in Table 1.

Table 1. Demographic characteristics, clinical parameters, and visit-level classifications

Characteristic / Clinical Parameter	Retrospective Patients (n=88)	Inpatient Visits (n=380)
Age (Years), Median (IQR) [Range]	5.0 (3.0–8.5) [1.0–18.0]	—
Body Weight (kg), Median (IQR)	17.5 (12.0–24.0)	—
Body Surface Area (m^2), Median (IQR)	0.72 (0.54–0.91)	—
Gender Distribution		
• Male	53 (60.23%)	232 (61.05%)
• Female	35 (39.77%)	148 (38.95%)
Leukemia Risk Stratification		
• Standard Risk (Risiko Biasa)	48 (54.55%)	214 (56.32%)
• High Risk (Risiko Tinggi)	40 (45.45%)	166 (43.68%)
Degree of Polypharmacy (Jonsdottir et al., 2024)		
• Non-Polypharmacy (< 5 drugs)	12 (13.64%)	48 (12.63%)
• Polypharmacy (5–9 drugs)	72 (81.82%)	317 (83.42%)
• Hyperpolypharmacy (≥ 10 drugs)	4 (4.55%)	15 (3.95%)
Length of Hospital Stay (Fitriani et al., 2016)		
• Short Stay (< 8 days)	84 (95.45%)	368 (96.84%)
• Extended Stay (≥ 8 days)	4 (4.55%)	12 (3.16%)

Categorization of polypharmacy according to Jonsdottir et al. (2024) revealed that polypharmacy (5–9 concurrent medications) was present in 317 visits (83.42%), hyperpolypharmacy (≥ 10 medications) in 15 visits (3.95%), and non-polypharmacy (< 5 medications) in 48 visits (12.63%). Thus, 87.37% of all inpatient visits involved 5 or more medications. Polypharmacy is virtually universal in pediatric leukemia management due to the complexity of protocol-driven multi-agent chemotherapy combined with essential supportive care drugs (Siregar et al., 2025). Furthermore, classification of length of stay according to Fitriani et al. (2016) demonstrated that 368 visits (96.84%) were short stays (< 8 days), while 12 visits (3.16%) were extended stays (≥ 8 days). The preponderance of short stays reflects the routine clinical workflow of scheduled short-stay admissions for chemotherapy administration.

Among the 380 retrospective visits, secondary medical conditions or complications were recorded in 89 visits (23.42%), yielding a total of 95 secondary condition events (certain visits presented with multiple concurrent conditions). A crucial finding arising from the detailed medical audit involves the clinical re-classification of oral mucosal lesions, historically labeled as recurrent mouth ulcer in

medical records. Oral mucositis accounted for 74 recorded events (76.29% of all secondary conditions), representing the single most frequent secondary diagnosis.

In accordance with modern pediatric oncology literature, oral mucositis in this population is appropriately characterized as a chemotherapy-induced adverse mucosal effect rather than an independent pre-existing comorbidity (Hu et al., 2024). Chemotherapeutic agents utilized in ALL protocols—most notably high-dose methotrexate (HD-MTX) and 6-mercaptopurine (6-MP)—exert direct cytotoxic damage on rapidly dividing oral mucosal epithelial cells. Methotrexate competitively inhibits dihydrofolate reductase (DHFR), interrupting purine and pyrimidine thymidylate synthesis, which induces mucosal cell arrest, desquamation, and severe painful ulceration (Hanoodi & Mittal, 2025; Hu et al., 2024). Furthermore, concomitant chemotherapy-induced neutropenia and thrombocytopenia secondary to bone marrow suppression exacerbate the risk of secondary microbial colonization and mucosal bleeding (Arifah, 2019). The breakdown of all recorded secondary conditions is detailed in Table 2.

Table 2. The breakdown of all recorded secondary conditions

No	Secondary Diagnosis / Condition	Frequency (n=95)	Percentage (%)
1	Oral Mucositis (Chemotherapy-Induced Adverse Effect)	74	77.89%
2	Pneumonia	4	4.21%
3	Gastroenteritis	4	4.21%
4	Colitis	4	4.21%
5	Acute Bronchitis	2	2.11%
6	Atrial Septal Defect (ASD)	1	1.05%
7	Dermatitis	1	1.05%
8	Constipation	1	1.05%
9	Cystitis	1	1.05%
10	Scabies	1	1.05%
11	Pyoderma	1	1.05%
12	Upper Respiratory Tract Infection (URTI)	1	1.05%
13	Hypo-osmolality and Hyponatremia	1	1.05%
14	Adjustment Disorder	1	1.05%
Total	**Total Recorded Secondary Condition Events**	**95**	**100.00%**

Calculation of percentage breakdown shows that 4 cases out of 95 secondary condition events represent 4.21%. True comorbidities, including infectious complications (pneumonia, gastroenteritis, colitis, bronchitis) and congenital/structural disorders (atrial septal defect), required targeted systemic antimicrobial, anti-inflammatory, or supportive therapies, thereby expanding the patient's pharmacological burden and elevating interaction risks (Tambun et al., 2025).

Analysis of vincristine pharmacotherapy revealed a total of 380 vincristine administration events across the 88 retrospective patients. In all instances (100%), vincristine was administered via intravenous (IV) bolus infusion over 5 minutes, diluted in 10 mL of 0.9% sodium chloride, adhering strictly to pediatric safety standards that prohibit intrathecal administration (Awosika et al., 2023; IDAI, 2018). Dosing was individualized based on Body Surface Area (BSA), calculated using the standard formula: BSA (m^2) = $\sqrt{}$[Height (cm) x Weight (kg) / 3600]. In accordance with the national

Indonesian Pediatric Hematology-Oncology protocol (IDAI, 2018), the standard prescribed dose was 1.5 mg/m² BSA, capped at a maximum single dose limit of 2.0 mg to mitigate severe neurotoxicity.

Distribution across active chemotherapy phases showed that vincristine was administered during Remission Induction in 117 visits (30.79%), Intensification/Consolidation in 26 visits (6.84%), Maintenance therapy in 167 visits (43.95%), and Transition/Unspecified outpatient continuation cycles in 70 visits (18.42%). Because vincristine serves as a non-myelosuppressive backbone agent in ALL protocols, its frequent administration during both intensive induction and prolonged maintenance exposes patients to potential drug interactions across all stages of leukemia therapy (Barnett et al., 2022; Katzung, 2023).

Retrospective screening utilizing the Lexidrug Interact database identified 12 potential drug-drug interaction pairs involving vincristine across 10 individual patients. At the visit level, potential DDIs were present in 12 out of 380 visits (prevalence = 3.16%). At the patient level, 10 out of 88 patients experienced at least one potential DDI (prevalence = 11.36%). Notably, 368 visits (96.84%) showed no potential vincristine interactions. All 12 identified interaction pairs (100%) were categorized as Moderate in clinical severity, Pharmacokinetic in mechanism, and assigned Lexidrug Risk Rating C (Monitor Therapy). No Major (Rating D/X) or Minor (Rating B) interactions involving vincristine were detected. The complete characteristics of identified potential DDIs are presented in Table 3.

Table 3. Characteristics of identified potential DDIs

Interacting Drug Pair	Visits (n=12)	Severity	Lexidrug Rating	Mechanism of Action	Management	Share (%)
Vincristine + Fluconazole	6	Moderate	Rating C	CYP3A4 Inhibition → Increased VCR AUC & Neurotoxicity	Monitor Toxicity	50.0%
Vincristine + Phenobarbital	3	Moderate	Rating C	CYP3A4 Induction → Decreased VCR AUC & Reduced Efficacy	Monitor Efficacy	25.0%
Vincristine + Metamizole	3	Moderate	Rating C	CYP3A4 Induction → Accelerated Clearance & Reduced AUC	Monitor Efficacy	25.0%

Vincristine + Fluconazole constituted 6 out of 12 interaction events (50.0%). Fluconazole is a moderate inhibitor of CYP3A4. Co-administration inhibits vincristine hepatic metabolism, increasing systemic vincristine AUC and peak plasma concentrations, thereby elevating the risk of severe peripheral neuropathy, constipation, and ileus (Heidari et al., 2023; Zekavat et al., 2025). Primary clinical studies demonstrate that azole antifungals combined with vinca alkaloids significantly increase neurotoxicity incidence compared to vincristine alone (Heidari et al., 2023). Regarding QT interval concerns, while fluconazole possesses intrinsic QT-prolonging potential, vincristine does not directly prolong cardiac repolarization; thus, QT monitoring is driven primarily by fluconazole therapy rather than a synergistic pharmacodynamic cardiac interaction (Drugs.com, 2026).

Vincristine + Phenobarbital accounted for 3 events (25.0%). Phenobarbital acts as a potent inducer of hepatic CYP3A4 and P-gp efflux transporters, accelerating vincristine metabolic clearance and lowering systemic plasma concentrations, which may attenuate antineoplastic efficacy (Lexidrug, 2026c). Vincristine + Metamizole (Dipyrone) comprised 3 events (25.0%). Metamizole acts as a moderate-to-strong inducer of CYP3A4 enzymes (Brinkman et al., 2025), enhancing vincristine hepatic metabolism and potentially lowering vincristine AUC.

Statistical evaluations were performed to analyze the relationship between patient clinical characteristics and potential DDI frequency. Non-parametric Spearman's Rank correlation demonstrated a statistically significant positive correlation between the degree of polypharmacy (total concurrent medications) and potential DDI frequency ($rs = 0.268$, $p < 0.001$). Similarly, length of hospital stay exhibited a statistically significant positive correlation with potential DDI frequency ($rs = 0.230$, $p < 0.001$). These correlations confirm that expanded medication regimens and prolonged hospitalizations increase the chemical exposure window, elevating interaction opportunities (Herdaningsih et al., 2023; Sari et al., 2023; Wannawichate & Limpawattana, 2023). To address reviewer feedback regarding contingency table testing and low expected cell counts, cross-tabulations were evaluated using both Pearson Chi-Square (χ^2) and Fisher's Exact Test. For Leukemia Risk Stratification (Standard Risk vs. High Risk), Pearson Chi-Square yielded $\chi^2 = 1.213$ ($df = 2$, $p = 0.545$) and Fisher's Exact Test yielded $p = 0.560$, confirming no statistically significant association between leukemia risk group and DDI frequency. Risk stratification dictates antineoplastic protocol intensity (e.g., higher chemotherapy doses), but DDI occurrence is governed by supportive care drugs and polypharmacy rather than leukemia risk group (DiPiro et al., 2023; IDAI, 2018).

For Comorbidities and Secondary Conditions (Absent vs. Present), Pearson Chi-Square yielded $\chi^2 = 7.530$ ($df = 2$, $p = 0.023$) and Fisher's Exact Test yielded $p = 0.008$, establishing a statistically significant association between the presence of secondary medical conditions and potential DDI frequency. Patients with secondary conditions required additional supportive anti-infective or symptomatic treatments, directly increasing medication count and interaction risks (Tambun et al., 2025). Detailed statistical testing parameters are presented in Table 4.

Table 4. Statistical testing parameters

Clinical Variable	Statistical Method	Value	df	Chi-Sq p	Fisher p
Total Concurrent Medications	Spearman Rank (rs)	0.268	—	**< 0.001***	**< 0.001***
Length of Stay (LOS)	Spearman Rank (rs)	0.230	—	**< 0.001***	**< 0.001***
Presence of Comorbidities	Pearson χ^2 / Fisher Exact	7.530	2	**0.023***	**0.008***
Leukemia Risk Stratification	Pearson χ^2 / Fisher Exact	1.213	2	0.545	0.560

Note: * indicates statistical significance at $p < 0.05$. Both non-parametric Spearman rank correlation and Fisher's exact test confirm that polypharmacy, length of stay, and secondary conditions are significantly associated with potential DDI frequency, whereas leukemia risk stratification shows no correlation.

The prospective concurrent monitoring phase comprised 41 unique patients generating 56 inpatient visits in the Wijayakusuma Ward during November–December 2025. Real-time screening identified 1 potential moderate DDI event involving vincristine and metamizole in a 3-year-old male High-Risk ALL patient with lagophthalmos admitted from December 4 to 9, 2025. Clinical observation during hospitalization showed stable vital signs without acute adverse manifestations. Laboratory monitoring parameters (complete blood count, hepatic enzymes [SGOT/SGPT], renal function [BUN/serum creatinine]) remained within acceptable limits for ongoing chemotherapy. Therapeutic drug monitoring (TDM) to quantify vincristine plasma AUC was not performed due to institutional laboratory resource constraints.

In addition, a targeted clinical audit of the retrospective medical records for the 6 patients with vincristine–fluconazole co-administration was conducted. Audit results revealed that 2 patients experienced mild, transient constipation managed successfully with oral laxatives. None of the patients developed severe peripheral neuropathy, motor weakness, paralytic ileus, SIADH-induced hyponatremia, or documented QT prolongation. This low rate of overt clinical toxicity suggests that

short-term co-administration of moderate CYP3A4 modulators may be tolerated in pediatric patients when vincristine dosing is capped at 2.0 mg and treatment duration is brief.

The visit-level potential DDI prevalence observed in this study (3.16%) is lower than overall DDI rates reported in general pediatric oncology literature, which frequently range from 40% to 78% (Ismail et al., 2020; Soccal et al., 2017; Zekavat et al., 2025). This difference is explained by our focused study scope: we specifically screened interaction pairs directly involving vincristine, whereas broad screening studies evaluate all possible pairwise drug combinations across the entire inpatient medication chart. When vincristine-specific pairs are isolated in broader studies, vincristine interaction rates are comparable to our findings.

Furthermore, evaluation of database agreement highlights known variations between compendia. While Lexidrug Interact categorizes vincristine–fluconazole as Moderate severity (Rating C), Stockley's Drug Interactions (Preston, 2019) emphasizes clinical monitoring for vinca alkaloid neurotoxicity, and Drugs.com (Drugs.com, 2026) classifies the pair as Moderate. Variations in severity grading across databases underscore the importance of utilizing multi-database screening protocols and establishing institutional clinical pharmacy surveillance (Shariff et al., 2022).

To maximize clinical relevance, hospital clinical pharmacists should implement routine pharmaceutical care protocols for pediatric ALL patients. When moderate CYP3A4 inhibitors (e.g., fluconazole) or inducers (e.g., phenobarbital, metamizole) must be co-administered with vincristine, structured clinical monitoring for peripheral neuropathy, deep tendon reflexes, bowel habits, and therapeutic efficacy should be systematically documented. Establishing collaborative clinical pharmacy services within pediatric oncology wards represents a high-value, cost-effective strategy to optimize chemotherapy safety (Barnett et al., 2022; Shariff et al., 2022).

CONCLUSION

In conclusion, this study demonstrates that potential drug-drug interactions involving vincristine at RSUD Prof. Dr. Margono Soekarjo Purwokerto occur at a visit-level prevalence of 3.16% (12 out of 380 visits) and a patient-level prevalence of 11.36% (10 out of 88 patients). All identified potential interactions were moderate in severity, pharmacokinetic in mechanism, and categorized as Lexidrug Risk Rating C (Monitor Therapy), involving co-administration with fluconazole (50.0%), phenobarbital (25.0%), and metamizole (25.0%). The degree of polypharmacy, length of hospital stay, and the presence of secondary medical conditions are significantly associated with potential DDI frequency, whereas leukemia risk stratification shows no significant association. Prospective clinical monitoring and retrospective chart audits confirmed that short-term potential interactions caused no severe clinical toxicities. Implementing routine clinical pharmacy monitoring and establishing multi-database interaction screening are recommended to maintain patient safety and optimize pediatric chemotherapy outcomes.

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