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Review Article

Understanding the Safety Profile of Imatinib in Asian Chronic Myeloid Leukemia Patients: A Systematic Review

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Abstract

Background: The treatment of chronic myeloid leukemia has advanced substantially since the introduction of tyrosine kinase inhibitors, particularly imatinib. However, adverse events associated with imatinib may affect adherence and quality of life, highlighting the importance of understanding safety outcomes across populations.
Objective: This systematic review aimed to synthesize evidence on hematologic and non-hematologic adverse events associated with imatinib use among chronic myeloid leukemia patients in Asia.
Methods: A systematic literature search was conducted in PubMed, Scopus, and ScienceDirect for studies published between January 2020 and July 2025. Eligible studies were synthesized narratively due to methodological heterogeneity. Adverse events were extracted as reported and graded using standardized toxicity criteria, and causality assessment was applied when available. Study quality was evaluated using established critical appraisal tools. Five studies from India, China, and Taiwan met the inclusion criteria.
Results: The most frequent hematologic adverse event was anemia, followed by neutropenia and thrombocytopenia. Common non-hematologic adverse events included gastrointestinal symptoms, peripheral or periorbital edema, muscle cramps, and hyperpigmentation, with regional variations. Most events were mild to moderate (grades 1–2), while severe fluid retention, including pleural and pericardial effusions, was reported in isolated cases. No studies reported permanent discontinuation of imatinib due to adverse events.
Conclusion: This review summarizes imatinib-related adverse events among chronic myeloid leukemia patients from selected Asian regions—East and South Asia, specifically India, China, and Taiwan—showing predominantly mild to moderate toxicities and providing practice-informed insights for clinical monitoring. However, the absence of data from other Asian regions precludes generalization to the entire Asian continent.

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INTRODUCTION

Chronic myeloid leukemia (CML) is a blood cancer characterized by a balanced translocation between chromosomes t(9;22)(q34;q11.2), creating the Philadelphia chromosome (Ph). This translocation fuses the breakpoint cluster region protein (BCR) of chromosome 22 and Abelson tyrosine protein kinase 1 (ABL1) of chromosome 9, resulting in the formation of the BCR-ABL1 fusion oncogene.[1] BCR-ABL1 induces uncontrolled tyrosine kinase activity, resulting in hematopoietic cell proliferation and leukemic transformation.[2] Imatinib, the first-generation tyrosine kinase inhibitor (TKI), has become the most widely used first-line therapy globally, including in Asia.[1,3] However, the genetic and pharmacogenetic characteristics of Asian populations often differ from those of non-Asian populations, potentially influencing the safety and toxicity profile of imatinib.[4] These variations underscore the importance of a systematic evaluation of imatinib-related adverse events (AEs) among Asian patients with CML to better understand the patterns, severity, and implications for long-term treatment continuity.

The latest Global Burden of Disease Analysis 2021 indicates a continued increase in the global prevalence of leukemia, accompanied by a decline in disability-adjusted life years (DALYs), with CML showing one of the most substantial reductions in DALYs between 1990 and 2021.[5] Consistent with these findings, estimates from GLOBOCAN 2022 reported approximately 487,000 new leukemia cases worldwide in 2022, with CML accounting for about 18% of adult leukemia cases and exhibiting considerable regional variation across Asian populations. Moreover, the incidence of CML remains higher in men than in women, with global age-standardized incidence rates of 1.5 per 100,000 and 1.0

per 100,000, respectively.[6] Despite overall improvements in survival, the decline in mortality has been more pronounced in developed countries, whereas CML-related mortality remains relatively high in developing regions.[7]

Chronic myeloid leukemia treatment has undergone a revolution from a fatal disease to a manageable chronic disorder following the development of targeted therapy with tyrosine kinase inhibitors (TKIs). Advances in TKI therapy have drastically changed the prognosis of CML and increased patient survival.[8] Imatinib, a first-generation TKI, was approved by the FDA in 2001 for CML therapy.[9] As of 2022, there are six TKIs available as options for CML treatment: imatinib, dasatinib, bosutinib, nilotinib, ponatinib, and asciminib.[1] Despite this, imatinib remains the most cost-effective first-line treatment for adult CML patients in many countries. Although second-generation TKIs offer clinical benefits, affordability remains a challenge in current healthcare systems, and therefore, they remain preferred as second-line treatment.[10]

Imatinib is generally not curative, so patients must continue taking the drug to maintain its benefits, except in a small minority of patients who achieve a deep molecular response (DMR).[11] Although imatinib's efficacy has been widely proven across various populations, its side effects are a factor that influences adherence to therapy. Therefore, managing side effects is crucial to maintaining adherence and improving patients' quality of life.[12,13] A study conducted by Adattini et al., found that 43% of patients experienced severe adverse drug reactions (grade ≥ 3) within the first 3 months of imatinib therapy. This was the main reason for dose reductions or temporary discontinuation of the drug.[14] However, adverse event profiles may vary across regions and ethnic groups, and evidence specific to Asian populations remains limited and fragmented.

In most clinical trials, no significant differences in TKI safety were reported between Asian and non-Asian subgroups or the overall study populations. However, a literature review by Kyriacou et al. identified distinct adverse-event patterns between Asian and non-Asian participants across multiple TKI trials.[15] Common hematological and non-hematological AEs included anemia and dermatologic changes.[7] Preliminary conference data from Southeast Asia suggest a broadly comparable imatinib safety profile, with relatively higher rates of weight gain, skin toxicity, and gastrointestinal symptoms.[16] To date, no systematic review has comprehensively summarized imatinib-related AEs and safety outcomes specifically among Asian patients with CML.

The number of CML cases in Asia continues to rise in absolute terms. Many developing Asian countries are only recently gaining broader access to TKIs. Despite therapies such as imatinib, they continue to face multiple challenges, including delayed diagnosis, limited drug availability, and the relatively high cost of treatment.[17] In this context, it is important to determine whether there are unique or more prominent adverse-event patterns in Asian populations compared with those reported in previously published global findings. A deeper understanding of these differences will not only strengthen adverse-event monitoring strategies but also support the adaptation of local clinical guidelines, improve patient adherence, and optimize treatment outcomes. Considering epidemiologic variability, differences in healthcare access, and the specific characteristics of patients across Asian regions, comprehensive mapping of imatinib's adverse-event profile is needed to ensure more contextual and targeted therapeutic management. Therefore, this systematic review aims to collect, identify, evaluate, and synthesize scientific evidence regarding imatinib-related adverse events as indicators of the safety profile among CML patients in Asian countries.

METHODS

Study Design

This study is a systematic review evaluating imatinib-related adverse events among patients with CML in Asian populations. The manuscript was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This review was not registered in PROSPERO because study selection and data extraction had been completed prior to registration. Nevertheless, all methodological steps were conducted according to a predefined protocol to minimize potential bias. The methodological quality of included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools according to study design.[18] Each article was independently evaluated, and studies were categorized as having low, moderate, or high methodological quality based on overall appraisal results.

Search strategy

An electronic literature search was conducted on 30 July 2025 across three major databases—Scopus, ScienceDirect, and PubMed— to identify publications from January 2020 to July 2025. The same search string was applied across all databases: ("Chronic Myeloid Leukemia" OR "CML") AND (imatinib) AND ("adverse effects" OR safety).

In Scopus, the search was limited to articles written in English, open-access publications, and studies originating from all Asian countries. In ScienceDirect, the filters included "research articles" and "case reports," English language, and both open access and open archive content. In PubMed, the filters were expanded to include various observational and experimental study designs such as adaptive clinical trials, clinical trials (Phase I–IV), controlled clinical trials, randomized controlled trials, observational studies, comparative studies, multicenter studies, case reports, case series, cross-sectional studies, cohort studies, case-control studies, twin studies, and validation studies. Additional restrictions were applied to include only English-language articles, free full-text availability, human subjects, and adult populations (>18 years). This approach was employed to ensure comprehensive yet relevant coverage for identifying all scientific reports describing adverse events of imatinib in CML patients across Asia. Medical Subject Headings (MeSH) terms were not explicitly applied in the PubMed search; however, equivalent free-text keywords (e.g., "chronic myeloid leukemia," "imatinib," and "adverse effects") were used to retrieve relevant indexed records. This strategy may have limited search sensitivity and is acknowledged as a methodological limitation.

Eligibility Criteria

Methodological consistency was maintained by formulating eligibility criteria based on the Population–Intervention–Comparison–Outcome (PICO) framework. The population included patients diagnosed with CML at any disease phase and residing in Asian countries. The intervention comprised the use of imatinib as monotherapy or in combination with agents that do not exhibit overlapping toxicity profiles—such as hydroxyurea during early treatment or placebo in clinical trials—provided that the study reported adverse events or safety data related to imatinib. Studies involving combination therapies with agents capable of producing independent toxicities were excluded to ensure accurate causal attribution to imatinib. No specific comparator was required; thus, studies with or without control groups were considered eligible. The outcomes encompassed all reported adverse events, toxicities, or safety concerns associated with imatinib use, including the frequency, type, and severity of events. The inclusion and exclusion criteria applied in this review are summarized in **Table 1**.

Table 1. Article inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1. Studies reporting imatinib-related adverse events and their severity in CML patients. 2. Studies conducted in Asian countries. 3. Observational studies and experimental studies. 4. English-language studies. 5. Publication Year 2020-2025. 6. Adult patients (> 18 years).	1. Studies not reporting imatinib-related adverse events or involving non-CML populations. 2. Reviews, editorials, abstracts, or articles without full text. 3. Animal or in vitro studies. 4. Pregnant or pediatric populations (≤ 18 years). 5. Studies evaluating combination regimens in which imatinib was not the primary treatment or involving agents with independent toxicity profiles and lacking a comparator arm (e.g., placebo or imatinib monotherapy).

Data Extraction

All retrieved records were imported into Mendeley Reference Manager for citation management and duplicate removal. Title and abstract screening, full-text eligibility assessment, and data extraction were performed manually by reviewers using standardized extraction forms. Data extracted from each eligible article included the publication title, authors, year of publication, country of origin, study design, sample size, age characteristics, comparator drugs (if available), imatinib dosage, types of adverse events, event frequency, severity graded according to the Common Terminology Criteria for Adverse Events (CTCAE) or other relevant instruments, and reported management strategies. Data extraction was conducted by four reviewers, with two reviewers independently performing the initial extraction and the remaining two serving as adjudicators in cases of discrepancies. This approach was applied to ensure data accuracy and consistency. To maintain uniformity across studies, all safety outcomes were collectively referred to as adverse events (AEs). In studies where formal causality assessment was performed, events were further classified as adverse drug reactions (ADRs); however, results were synthesized and presented primarily as AEs due to heterogeneity in causality assessment across included studies.

Data Analysis

Studies that met the eligibility criteria were analyzed using a narrative synthesis approach due to methodological heterogeneity across included studies. Adverse events were extracted as reported and graded primarily using the Common Terminology Criteria for Adverse Events (CTCAE), including versions 4.0, 4.03, and 5.0. In studies where formal causality assessment was available (e.g., WHO–UMC or Naranjo algorithm), events were classified as adverse drug reactions; otherwise, adverse events temporally associated with imatinib exposure were synthesized. To address variability in grading systems across studies, severity categories were harmonized by grouping grades 1–2 as mild to moderate events and grades 3–4 as severe events, in accordance with standard clinical oncology practice. Findings were presented descriptively and summarized in tables reporting study characteristics, methodological quality, and hematologic and non-hematologic adverse events with severity grades. A meta-analysis was not conducted because the required methodological homogeneity was not met.

RESULT

Study Selection

The study selection process is summarized in **Figure 1**. After screening and eligibility assessment, five studies were included in the final review.

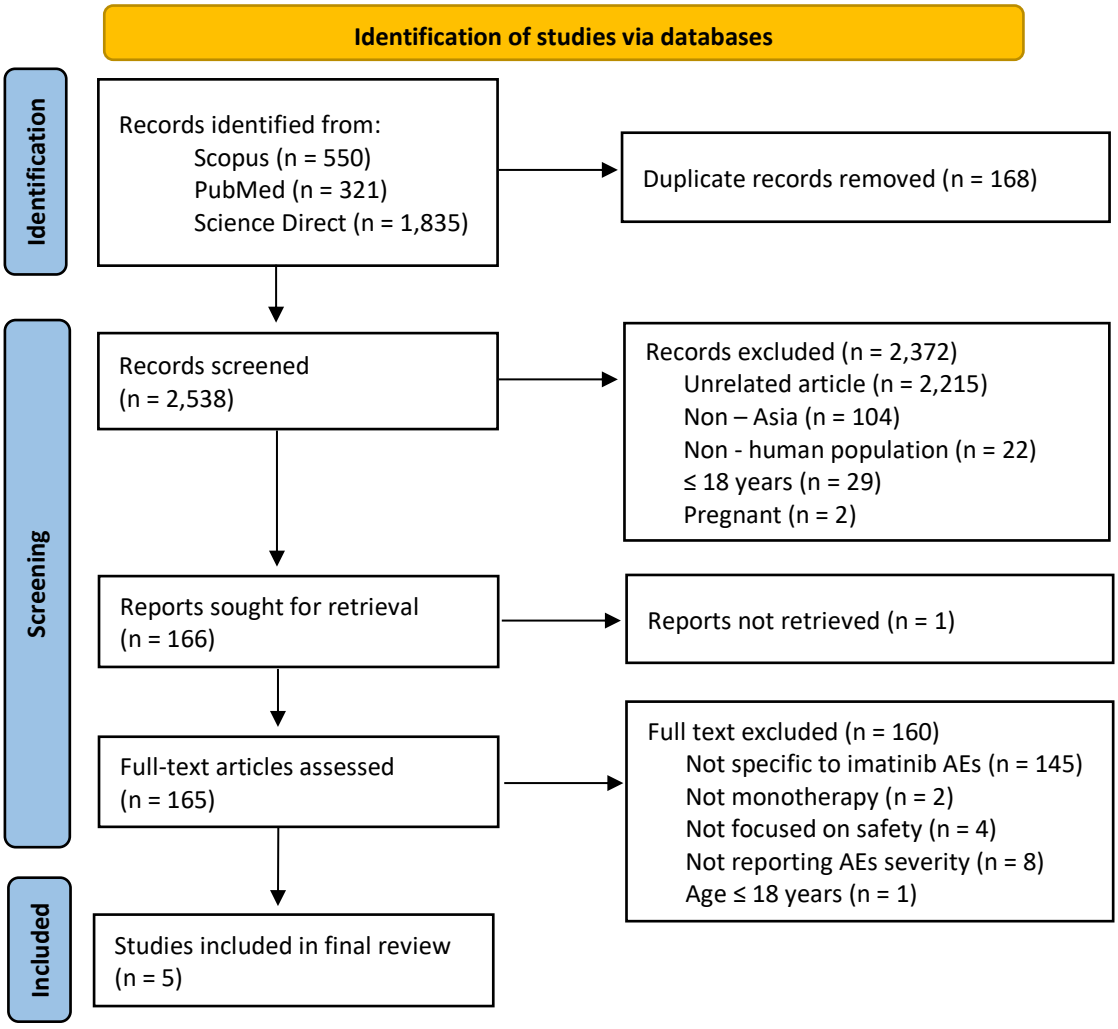

Figure 1. PRISMA flow diagram for study selection

Characteristics of Included Studies

A total of five studies were included in this systematic review, comprising two randomized controlled trials, two cohort studies, and one case report. The studies were conducted in three Asian countries—India, China, and

Taiwan—representing South and East Asian populations, with sample sizes ranging from 1 to 310 participants. All included studies evaluated imatinib-based therapy in adult patients with CML. Adverse events were assessed using CTCAE grading systems (versions 4.0, 4.03, and 5.0) in four studies, while one case report applied clinical assessment. Detailed characteristics of the included studies are presented in **Table 2**.

Table 2. Characteristics of included studies

Study	Country	Design	N	Intervention	AEs grading system
Swain et al. (2022)[19]	India	Prospective observational cohort	310	Imatinib	CTCAE v4.03 and modified Hartwig–Siegel severity scale
Su et al. (2022)[20]	Taiwan	Case report	1	Imatinib	Clinical assessment
Cheng et al. (2023)[21]	China	Long-term cohort	237	Imatinib	CTCAE v4.0
Bandyopadhyay et al. (2023)[22]	India	Double-blind randomized controlled trial	62	Imatinib with vitamin D_3 versus Imatinib with placebo	CTCAE v5.0
Chetia et al. (2025)[23]	India	Open-label randomized controlled trial	90	Imatinib with hydroxyurea versus Imatinib	CTCAE v5.0

Methodological Quality of Included Studies

The methodological quality and causality assessment of the included studies are summarized in **Table 3**. Two studies were rated as high quality, while three demonstrated moderate methodological quality. Formal causality assessment was performed in two studies, which reported adverse drug reactions, whereas the remaining studies reported adverse events without causal attribution.

Table 3. Methodological quality and causality assessment

Study	JBI quality	Causality assessment	Reported outcome
Swain et al. (2022)[19]	Moderate	WHO–UMC	ADRs
Su et al. (2022)[20]	High	Naranjo	ADRs
Cheng et al. (2023)[21]	Moderate	Not performed	AEs
Bandyopadhyay et al. (2023)[22]	High	Not performed	AEs
Chetia et al. (2025)[23]	Moderate	Not performed	AEs

Hematologic Adverse Events

Hematologic adverse events are summarized in **Table 4**. Anemia was consistently the most frequently reported hematologic AE across included studies, followed by leukopenia, neutropenia, and thrombocytopenia. Most hematologic AEs were mild to moderate (grades 1–2), with grade 3–4 events accounting for a small proportion. Severe cytopenias were uncommon, and permanent discontinuation of imatinib due to hematologic toxicity was not reported.

In the Eastern Indian cohort (n = 310), hematologic adverse events accounted for 42.6% of all AEs (509 events). Anemia was the most common hematologic toxicity, representing 41.3% of hematologic AEs (198 grade 1–2 cases and 12 grade 3–4 cases), followed by leukopenia (21.5%), lymphopenia (20.4%), neutropenia (10.6%), and thrombocytopenia (6.2%). Most hematologic AEs were grade 1–2, with only 60 events classified as grade 3–4, comprising 5% of all reported AEs. The mean time to onset of hematologic toxicity was 12.5 weeks for grade 1–2 events and 17 weeks for grade 3–4 events.[19]

In the Chinese cohort (n = 237) with a median follow-up duration of 6.5 years, hematologic adverse events included anemia in 54.0% of patients (any grade), followed by leukopenia (32.5%), thrombocytopenia (28.3%), and neutropenia (21.9%). Neutropenia (9.3%) and anemia (7.6%) were the most frequently observed grade 3–4 hematologic AEs. The majority of cases were grade 1–2, with only a small proportion classified as grade 3–4. Nearly all events were manageable with supportive care or short-term dose modifications, and permanent discontinuation of imatinib was rarely required.[21]

Table 4. Hematologic adverse events of imatinib in Asian CML patients

Study	Country	Design	N	Hematologic Adverse Events	Grade 1 - 2 N	Grade 3 - 4 N
Swain et al. (2022)[19]	India	Prospective observational cohort	310	Anemia Leukopenia Lymphopenia Neutropenia Thrombocytopenia	198 91 87 45 28	12 18 17 9 4
Su et al. (2022)[20]	Taiwan	Case report	1	Leukopenia Neutropenia	1 1	
Cheng et al. (2023)[21]	China	Long-term cohort	237	Anemia Leukopenia Thrombocytopenia Neutropenia	110* 68* 52* 30*	18 9 15 22
Bandyopadhyay et al. (2023)[22]	India	Double-blind randomized controlled trial (Imatinib with vitamin D_3 vs Imatinib with placebo)	62	Anemia Leukopenia Thrombocytopenia Febrile neutropenia	6* vs 6* 4* vs 3* 2* vs 4* 0* vs 0*	1 vs 2 0 vs 0 0 vs 0 1 vs 1
Chetia et al. (2025)[23]	India	Open-label randomized controlled trial (Imatinib with hydroxyurea vs Imatinib)	90	Anemia Leukopenia Neutropenia Thrombocytopenia Febrile neutropenia	39* vs 37* 23* vs 21* 13* vs 10* 27* vs 21* 0* vs 0*	2 vs 2 1 vs 1 1 vs 0 2 vs 1 2 vs 1

Information: * The N values for Grades 1-2 are calculated from the Any Grade data minus Grade 3-4

In the randomized trial comparing imatinib plus vitamin D_3 (IMVD) with imatinib plus placebo (IMP) (n = 62), anemia occurred in 7 patients (22.6%) in the IMVD group and 8 patients (25.8%) in the IMP group, with grade ≥3 events reported in 1 and 2 patients, respectively. Leukopenia was documented in 4 patients (12.9%) versus 3 patients (9.7%), thrombocytopenia in 2 patients (6.5%) versus 4 patients (12.9%), and neutropenic fever in one patient in each group, with one grade ≥3 event reported in both groups. No patients were withdrawn from the trial due to hematologic toxicity, and no significant differences were observed between groups during the 3-month follow-up period.[22]

Similarly, in the open-label randomized trial comparing imatinib plus hydroxyurea (I-HU) with imatinib monotherapy (IM), hematologic adverse events were common but predominantly mild. Thrombocytopenia occurred in 29 patients (64%) in the I-HU group and in 22 patients (49%) in the IM group. Leukopenia was reported in 24 patients (53%) versus 22 patients (49%), while neutropenia occurred in 14 patients (31%) versus 10 patients (22%). Anemia was documented in 41 patients (91%) versus 39 patients (87%) in the I-HU and IM groups, respectively, with a total of 80 patients experiencing hematologic AEs across the study. Several grade ≥3 hematologic AEs were recorded, including febrile neutropenia (4% vs. 2%), thrombocytopenia (4% vs. 2%), anemia (4% in each group), and neutropenia (2% in the I-HU group). No patient permanently discontinued therapy due to hematologic toxicity.[23] Overall, these findings suggest that hematologic toxicity associated with imatinib in Asian CML patients is generally manageable, with anemia representing the predominant manifestation.

Non-Hematologic Adverse Events

Non-hematologic adverse events are summarized in **Table 5**. Across included studies, gastrointestinal symptoms, fluid retention (peripheral or periorbital edema), muscle cramps, and dermatologic manifestations were the most frequently reported non-hematologic toxicities. Regional variation was observed, with cutaneous hyperpigmentation predominating in the Indian cohort, whereas fluid retention was more common in the Chinese cohort. Most non-hematologic AEs were mild to moderate (grades 1–2), while grade 3–4 events were uncommon. No study reported permanent discontinuation of imatinib due to non-hematologic AEs.

In the Eastern Indian cohort, non-hematologic adverse events predominated, accounting for 57.4% of all AEs (684 of 1,193 events). Cutaneous hyperpigmentation was the most frequently reported non-hematologic toxicity, affecting 26.6% of patients (174 mild-to-moderate cases and 8 severe cases). Other dermatologic manifestations included pruritus (9.9%), skin rash (8.4%), hypopigmentation (1.9%), and dry skin (6.4%). Periorbital and peripheral edema were reported in 8.1% and 8.0% of patients, respectively. Gastrointestinal complaints included nausea/vomiting (11.1%), abdominal pain (2.0%), diarrhea (3.2%), and hyperacidity (7.3%). Systemic symptoms such as headache or myalgia occurred in 4.0% of patients. Hypertension was observed in 1.3% of patients and had a higher proportion of severe cases compared with other AEs. Based on the Hartwig and Siegel severity scale, 51.6% of non-hematologic AEs were categorized as mild, 38.6% as moderate, and 9.8% as severe.[19]

In the Chinese cohort, non-hematologic adverse events occurred more frequently than hematologic ones. Fluid retention, particularly peripheral and periorbital edema, was the most commonly reported AE, occurring in approximately 34.2% of patients. These symptoms typically emerged within the first year of therapy. Other non-hematologic AEs included skin rash (19%); gastrointestinal symptoms such as nausea, diarrhea, or abdominal pain (approximately 15%); and dyslipidemia (19.8%). Most events were grade 1–2. Rash was the most frequently reported grade 3–4 non-hematologic AE (4.2%).[21]

In the randomized trial comparing imatinib plus vitamin D_3 with imatinib plus placebo, non-hematologic adverse events commonly included nausea/vomiting (32.3% vs. 29.0%), muscle cramps (25.8% in both groups), fluid retention (25.8% vs. 19.4%), stomatitis (12.9% vs. 22.6%), diarrhea (16.1% vs. 12.9%), and other complaints such as headache and hyperpigmentation, both of which were infrequently reported. Most events were grade 1–2; sporadic grade ≥3 events occurred for nausea/vomiting and muscle cramps. There were no significant differences in non-hematologic AEs between the two groups ($p = 0.6$), and no treatment discontinuation was required due to adverse events.[22]

Similarly, in the open-label randomized trial comparing imatinib plus hydroxyurea with imatinib monotherapy, non-hematologic adverse events primarily consisted of gastrointestinal symptoms, followed by muscle cramps, skin rash, and peripheral or periorbital edema. All non-hematologic AEs were mild-to-moderate in severity (grade 1–2), and no grade ≥3 serious events were observed. No treatment discontinuation occurred due to non-hematologic AEs during the follow-up period.[23] Overall, non-hematologic AEs associated with imatinib in Asian CML patients were predominantly mild and manageable, with regional differences observed in dominant toxicity patterns.

Table 5. Non-hematologic adverse events of imatinib in Asian CML patients

Study	Country	Design	N	Non-Hematologic Adverse Effects	Grade 1 – 2 N	Grade 3 – 4 N
Swain et al. (2022)[19]	India	Prospective observational cohort	310	Hyperpigmentation	174	8
				Nausea & Vomiting	76	0
				Pruritus	56	12
				Lid swelling	54	2
				Leg swelling	52	3
				Hyperacidity	49	1
				Skin rash	46	12
				Dry skin	44	0
				Headache & muscular pain	24	4
				Diarrhea	20	2
				Hypopigmentation	13	0
				Abdominal Pain	12	2
				Hypertension	6	3
Su et al. (2022)[20]	Taiwan	Case report	1	Massive pleural/pericardial effusion; Grade 4 fluid retention, cardiac tamponade		1

Study	Country	Design	N	Non-Hematologic Adverse Effects	Grade 1 – 2 N	Grade 3 – 4 N
Cheng et al. (2023)[21]	China	Long-term cohort	237	Periorbital and limb edema	72*	9
				Dyslipidemia	45*	2
				Diarrhea	42*	5
				Rash	35*	10
				Hepatobiliary dysfunction	41*	2
				Hyperuricemia	39*	1
				Musculoskeletal pain	27*	8
				Headache	24*	2
				Hyperglycemia	20*	0
				Nausea and vomiting	18*	3
				Fatigue	17*	2
				Gastrointestinal discomfort	15*	2
				Renal insufficiency	13*	0
				Skin whitening	12*	0
				Conjunctival hemorrhage	5*	0
Bandyopadhyay et al. (2023)[22]	India	Double-blind randomized controlled trial (Imatinib with vitamin D_3 vs Imatinib with placebo)	62	Nausea/vomiting	9* vs 7*	1 vs 2
				Muscle cramps	6* vs 7*	2 vs 1
				Fluid retention	8* vs 6*	0 vs 0
				Anxiety	7* vs 4*	0 vs 1
				Stomatitis/mouth ulcer	3* vs 7*	1 vs 0
				Diarrhea	5* vs 3*	0 vs 1
				Headache	2* vs 4*	0 vs 0
				Hyperpigmentation	1* vs 1*	0 vs 0
Chetia et al. (2025)[23]	India	Open-label randomized controlled trial (Imatinib with hydroxyurea vs Imatinib)	90	Nausea/vomiting	19* vs 16*	1 vs 1
				Muscle cramps	13* vs 13*	2 vs 0
				Hypopigmentation	7* vs 6*	0 vs 0
				Edema	5* vs 3*	1 vs 1
				Hyperpigmentation	5* vs 4*	0 vs 0
				Diarrhea	3* vs 2*	1 vs 0
				Stomatitis/Mouth ulcer	2* vs 2*	1 vs 0

Information: * The N values for Grades 1-2 are calculated from the Any Grade data minus Grade 3-4

Severe and Rare Adverse Events

Severe and rare adverse events, summarized in **Tables 4** and **Table 5**, were reported in a single case. Following four years of imatinib therapy, dose escalation to 600 mg/day was associated with grade 2 leukopenia and neutropenia, which improved after dose reduction to 400 mg/day without accompanying anemia or thrombocytopenia. The patient subsequently developed *Campylobacter jejuni* bacteremia, suggesting increased susceptibility to opportunistic infection. A serious non-hematologic AE involving massive fluid retention—including bilateral pleural and pericardial effusions—was also observed after dose escalation, presenting with dyspnea, lower-limb edema, rapid weight gain, and radiologic evidence of cardiomegaly and pleuropericardial fluid accumulation. Causality assessment using the Naranjo algorithm yielded a score of 9, indicating a definite causal relationship between imatinib exposure and these ADRs.[20]

DISCUSSION

Regional Variability and Safety Overview

Although this review identified patterns in the frequency and severity of adverse events, comparisons across regions and populations were based on indirect evidence derived from heterogeneous study designs and reporting frameworks. Therefore, any observed differences in adverse-event patterns should be interpreted with caution, as they may be influenced by variations in study methodology, patient characteristics, and healthcare settings rather than true regional or ethnic differences.

Imatinib mesylate, a first-generation tyrosine kinase inhibitor, remains the cornerstone therapy for chronic-phase chronic myeloid leukemia (CML-CP) worldwide, including in Asia.[24] The overall safety and tolerability profile of imatinib, established over more than two decades of clinical use as a targeted therapeutic agent for CML and other malignancies, has been widely documented and is generally well accepted in clinical practice. Nevertheless, despite this long-standing and robust evidence base, the occurrence of AEs continues to be a clinically relevant concern, particularly within patient populations whose pharmacogenetic characteristics and socioeconomic conditions differ substantially

from those typically represented in the original pivotal trials. To better elucidate the spectrum of AEs reported in selected Asian populations, this systematic review synthesizes and critically evaluates evidence derived from five independent studies conducted in India, China, and Taiwan, each employing distinct research methodologies, including prospective cohort studies, randomized controlled trials, and individual case reports. Collectively, these diverse sources of evidence offer a broad and detailed characterization of both commonly encountered toxicities and relatively rare but clinically significant AEs associated with imatinib therapy in these regions. The insights derived reveal patterns that appear consistent across studies as well as unique observations specific to certain locales. These findings may help inform context-specific clinical decision-making, guide patient counseling, and support the optimization of therapeutic strategies in settings characterized by distinct genetic backgrounds and healthcare resource constraints.

Non-Hematologic Adverse Events

There are differences in the adverse-event patterns between the Chinese and East Indian populations, particularly in terms of the most common non-hematological adverse events. The most striking difference in the non-hematological AEs profiles between the Chinese and East Indian populations is seen in the most frequently reported complaints. In a long-term cohort study in China, fluid retention, primarily periorbital edema and extremity edema, emerged as the most common non-hematological AEs, reported in 34.2% of patients.[21] This pattern contrasts with findings from a prospective study in East India, where skin hyperpigmentation was the most frequently reported non-hematological AE, accounting for 26.6% of all non-hematological AEs. Indian researchers have suggested that the high incidence of hyperpigmentation may be influenced by genetic factors, melanocyte variations, and environmental factors such as photosensitivity, which do not completely mirror the patterns seen in the Chinese population.[19] The mechanism of hyperpigmentation is thought to be related to stimulation of tyrosinase activity and modulation of melanogenesis pathways, including imatinib's effects on c-KIT and microphthalmia-associated transcription factor (MITF).[25] Furthermore, although fluid retention was also found in India, it was much lower in frequency. For example, eyelid swelling (8.1%) and leg swelling (8.0%) did not dominate the spectrum of AEs as in the Chinese study.[19] These differences suggest regional variations in the manifestations of imatinib toxicity, which may be influenced by genetic, lifestyle, and environmental factors, as well as differing clinical monitoring practices in each country.

Hematologic Adverse Events

Analysis of hematologic adverse-event patterns showed consistency between the two populations, with anemia emerging as the most commonly reported hematological adverse event in both the long-term follow-up study in China and the prospective study in East India. Although absolute frequencies cannot be directly compared due to differences in reporting methods, these findings confirm that anemia is the dominant manifestation of hematological toxicity with imatinib in both countries. Differences were observed in grade 3–4 toxicities, with the Chinese study identifying neutropenia as the most frequent severe event (9.3%), while the East India study predominantly reported leukopenia as the most common severe AE numerically, followed by lymphopenia and anemia.[19,21] This variation is likely influenced by differences in patient characteristics, monitoring patterns, and the AE classifications used, but overall, it still suggests that myeloid suppression is the primary mechanism of toxicity of imatinib in Asian populations. These findings are in line with the broader literature and reinforce that although imatinib is generally well tolerated, cytopenias remain a major cause of AEs due to its myelosuppressive properties.[26,27]

Severe and Rare Adverse Events

The leukopenia and neutropenia described in the case reported by Su et al. are likely related to the pharmacologic action of imatinib, which inhibits the BCR-ABL tyrosine kinase pathway. This, in addition to targeting leukemia cells, also interferes with the proliferation and maturation of normal hematopoietic cells. Imatinib also has off-target effects on c-kit and PDGFR, which can reduce immune cell function, including monocyte counts and macrophage phagocytosis. This decreased immune function can increase the risk of opportunistic infections, such as *Campylobacter jejuni* bacteremia in this case. Massive fluid retention in the form of pleural and pericardial effusions is a rarely reported AE of imatinib, especially compared with second- or third-generation TKIs. Possible mechanisms involved include imatinib's effect on PDGFR, which plays a role in regulating vascular permeability. Additional risk factors, such as dose escalation, acute infection, or pharmacokinetic changes such as increased α1-acid glycoprotein during the inflammatory phase, can exacerbate fluid accumulation. This case demonstrates that serious AEs can occur

even after long-term use that was previously well tolerated, and that physiological stressors such as infection can exacerbate the risk of fluid retention.[20]

Clinical Implications and Long-Term Safety

Overall, both studies demonstrated that imatinib had a similar safety profile and was generally well tolerated among patients from China and East India, although the dominant types of adverse events differed. Most AEs reported in both study populations were mild-to-moderate (grade 1–2), with only a small proportion reaching severe grades. In the East Indian study, only 9.8% of AEs were classified as severe, while the Chinese study reported 110 grade 3–4 events out of a total of 795 AEs, reaffirming that the majority of AEs were not severe.[19,21] The Chinese cohort reported that adverse events occurred most frequently during the first year of treatment and gradually declined over time.[21] This temporal pattern has also been observed in long-term clinical trials, including the pivotal IRIS study, which demonstrated that imatinib-related serious adverse events were most common in the initial year of therapy and decreased thereafter, with no emerging safety concerns observed throughout 10 years of follow-up.[28] Such trends are also aligned with contemporary dose-optimization strategies that aim to preserve therapeutic efficacy while improving long-term tolerability, as discussed by Jabbour and Kantarjian.[29] Differences in dominant patterns, such as more frequent hyperpigmentation reported in East Indian patients and more pronounced fluid retention in Chinese patients,[19,21] may reflect differential biological responses to the same therapy—likely influenced by genetic variation, environmental factors, or differences in clinical monitoring practices.[30] Nevertheless, both studies indicated predominantly mild to moderate AEs, with a relatively low proportion of severe toxicity in patients from the included studies.

Although the primary results of this systematic review are based mainly on clinical studies from India, China, and Taiwan, global pharmacovigilance data can provide additional perspectives regarding the potential long-term toxicities of imatinib. In this context, findings from the FAERS analysis[31] indicate that most serious AEs (84.24%) occur after more than 360 days of treatment, suggesting a cumulative risk that may not be fully captured in short-duration clinical studies. Beyond the well-recognized AEs, FAERS also identified several new safety signals—including delayed pubertal maturation, ototoxicity, pregnancy-related complications, joint ankylosis, and avascular necrosis—that are not consistently documented in early clinical trials or the Summary of Product Characteristics (SPC). These findings underscore the need for comprehensive long-term monitoring, encompassing endocrine, musculoskeletal, metabolic, dermatologic, and auditory evaluations, to ensure the ongoing safety of imatinib therapy.

Therefore, the findings of this review should be interpreted as reflecting safety data derived from clinical studies conducted in India, China, and Taiwan, rather than representing the entire Asian population. Differences in genetic background, healthcare systems, and treatment practices across Asia should be considered when applying these findings to other regions.

Limitation

This review has several limitations that should be considered when interpreting the findings. First, the geographic representation of the included studies was limited to India, China, and Taiwan. As previously acknowledged, this restricts the generalizability of the findings to other Asian regions, where genetic, environmental, and healthcare system factors may differ. Second, the included studies varied widely in design, ranging from randomized controlled trials to observational cohorts and a single case report, resulting in methodological heterogeneity. Although the randomized trials generally demonstrated low to moderate risk of bias, the observational studies exhibited important limitations, including unadjusted confounding, variable treatment durations, and treatment switching, which may influence the accuracy of adverse-event estimates. The case report contributed valuable clinical insight but is inherently at very high risk of bias and cannot be generalized. Third, inconsistencies in adverse-event assessment and reporting (e.g., differing CTCAE versions, incomplete grading, and heterogeneous monitoring schedules) may have led to under- or over-estimation of specific toxicities. Fourth, limiting the review to English-language publications and the absence of a prospectively registered protocol introduce potential publication and selection bias. Finally, formal causality assessment was performed in only two studies, limiting attribution of adverse events directly to imatinib. Nevertheless, the synthesis consolidates safety data on imatinib from India, China, and Taiwan, and highlights consistent patterns of hematologic and non-hematologic toxicities across study types. These findings provide a foundation for future research aimed at including underrepresented Asian populations and harmonizing adverse event reporting methodologies to enable more robust cross-regional comparisons.

CONCLUSION

This systematic review provides a narrative synthesis of hematologic and non-hematologic adverse events associated with imatinib use among CML patients from selected Asian countries. The observed adverse-event patterns were generally aligned with previously reported global evidence, with most events being manageable through supportive care and dose adjustment. These findings may help inform clinical monitoring, practices, and patient counseling in settings represented by the included studies, particularly regarding early recognition of common toxicities and adherence support. However, given the heterogeneity of included studies and the narrative nature of this review, these implications should be interpreted as practice-informed considerations rather than definitive evidence-based recommendations. Future research should prioritize multicenter prospective studies with standardized adverse-event grading and uniform monitoring approaches across diverse Asian regions. Pharmacogenomic investigations are also warranted to clarify the influence of regional genetic variability on imatinib metabolism and toxicity. In addition, long-term real-world data, including post-marketing surveillance and patient registries, are needed to better characterize chronic and rare adverse drug reactions.

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AUTHOR CONTRIBUTION STATEMENT

Niky Budiarti: Conceptualization, Methodology, Data Extraction, Writing – Original Draft; **Zullies Ikawati**: Supervision, Writing – Review & Editing; **Arief Nurrochmad**: Supervision, Writing – Review & Editing; **Thendi Abdul Arief**: Data Extraction, Writing – Original Draft.

CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest.

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