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Review

Hematopoietic Effects of Chemotherapy in Pediatric Patients with Acute Lymphoblastic Leukemia: A Systematic Review

[1]Danny Meganingdyah Primartati, [2]Aulia Risqi Fatmariza

[1,2] Faculty of Health Technology and Management, Institut Ilmu Kesehatan Bhakti Wiyata, Kediri, Indonesia

E-mail Corresponding: danny.mp@iik.ac.id

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ABSTRACT

Background: Chemotherapy is the mainstay of treatment for pediatric acute lymphoblastic leukemia (ALL) but is frequently associated with significant hematopoietic suppression. This systematic review aimed to evaluate the effects of chemotherapy on hematopoietic suppression and recovery in pediatric patients with acute lymphoblastic leukemia.

Methods: This systematic review was registered in PROSPERO (CRD420251074627) and conducted according to PRISMA 2020 guidelines. Literature searches were performed in PubMed, ScienceDirect, and SpringerLink for studies published between 2020 and 2025. Original studies assessing chemotherapy-related hematopoietic changes in pediatric ALL were included. After screening titles, abstracts, and full texts, 7 studies were eligible and synthesized narratively.

Results: Induction chemotherapy consistently caused profound suppression of erythropoiesis, granulopoiesis, and thrombopoiesis, reflected by declines in hemoglobin, absolute neutrophil counts, and platelet counts. Hematopoietic recovery was phase-specific and lineage-dependent, with earlier erythroid recovery compared with neutrophil and platelet recovery. Early markers, including reticulocyte indices and immature platelet fraction, demonstrated earlier recovery than conventional blood counts. Bone marrow assessments showed delayed restoration of marrow cellularity and hematopoietic stem cell compartments despite morphologic remission.

Conclusion: Chemotherapy-induced hematopoietic suppression in pediatric ALL is marked and heterogeneous, with recovery extending beyond morphologic remission. Integrated monitoring using peripheral blood parameters, early recovery markers, and selective bone marrow evaluation may improve assessment of hematopoietic recovery and supportive care during treatment.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic malignancy characterized by the uncontrolled proliferation of lymphoid progenitor cells at various stages of differentiation. It represents the most common pediatric cancer, accounting for approximately 25–30% of all childhood malignancies worldwide[1]. The disease originates from the accumulation of immature lymphoblasts within the bone marrow and may extend to peripheral blood and extramedullary tissues[2].

In pediatric patients, ALL profoundly disrupts normal hematopoiesis, leading to reductions across multiple blood cell lineages. This disruption manifests clinically as anemia, recurrent or opportunistic infections, and an increased risk of bleeding due to thrombocytopenia[3]. These abnormalities arise from both leukemic infiltration of the bone marrow and the suppression of normal hematopoietic progenitors, culminating in bone marrow failure and systemic complications[4].

Advances in risk-adapted chemotherapy protocols have dramatically improved survival outcomes for children with ALL, with cure rates exceeding 85% in high income countries[5]. Contemporary treatment regimens comprise multiple sequential phases including induction, consolidation, intensification, and maintenance which may extend over a period of up to three years. While these regimens are highly effective in eradicating leukemic blasts, they exert substantial cytotoxic effects on the hematopoietic system[6].

The hematopoietic system is organized as a dynamic hierarchy of hematopoietic stem cells (HSCs), multipotent progenitors, and lineage committed precursors that give rise to erythroid, myeloid, and lymphoid cells[7]. In children, hematopoiesis is highly active within the bone marrow, rendering it particularly vulnerable to cytotoxic injury from chemotherapy agents designed to target rapidly dividing cells[8]. Consequently, chemotherapy induced myelosuppression frequently presents as pancytopenia, accompanied by heightened susceptibility to infections, hemorrhagic complications, and increased dependence on transfusion support[9].

Importantly, chemotherapy related hematopoietic toxicity is not uniform across cell lineages. Several agents commonly used in ALL treatment protocols including anthracyclines, vincristine, and corticosteroids have been associated with lineage-specific and, in some cases, persistent hematopoietic impairment[10]. Moreover, hematopoietic recovery following chemotherapy is influenced by multiple patient and treatment related factors, such as age, baseline marrow reserve, pharmacogenomic variability, treatment intensity, and the quality of supportive care provided[11].

The clinical consequences of myelosuppression extend beyond laboratory abnormalities. Severe or prolonged cytopenias may necessitate treatment delays, dose reductions, or therapy interruptions, all of which can compromise treatment efficacy and adversely affect long-term outcomes[12]. Despite its clinical significance, existing literature predominantly addresses isolated hematologic parameters such as neutropenia duration or infection risk without integrating these findings into a comprehensive framework that captures the dynamic nature of hematopoietic suppression and recovery across different chemotherapy phases[13].

This fragmented approach highlights a critical gap in the literature, the absence of a holistic synthesis that evaluates chemotherapy induced hematopoietic dysfunction in pediatric ALL as a dynamic, lineage-specific, and phase dependent process. A clearer understanding of the degree, duration, and recovery kinetics of hematopoietic suppression is essential for optimizing supportive care strategies, minimizing treatment-related morbidity, and preserving treatment intensity. Furthermore, as survival rates continue to improve, long-

term hematopoietic sequelae such as persistent cytopenias, marrow hypoplasia, and secondary malignant neoplasms have emerged as important considerations within survivorship care paradigms[14,15].

Therefore, this systematic review aims to synthesize available evidence on the hematopoietic effects of chemotherapy in children with ALL, with a particular focus on lineage-specific suppression, recovery kinetics, and their clinical implications. By addressing existing knowledge gaps and integrating findings across treatment phases, this review seeks to provide a comprehensive evidence base to inform risk-adapted supportive care, guide clinical decision-making, and support long-term surveillance strategies in this vulnerable population.

METHOD

Methods and Criteria

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251074627. Registration was completed prior to data extraction and analysis to enhance methodological transparency and minimize the risk of bias.

A comprehensive literature search was conducted using three electronic databases: PubMed, ScienceDirect, and SpringerLink. The search targeted studies published between 2020 and 2025 that examined the hematopoietic effects of chemotherapy in pediatric patients with acute lymphoblastic leukemia (ALL). Study selection and reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and reproducibility.

The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to hematopoietic alterations and chemotherapy in pediatric ALL. Search terms included *"hematopoietic effects," "hematopoietic suppression," "hematopoietic recovery," "bone marrow suppression," "myelosuppression," "cytopenia,"* and *"hematologic toxicity,"* combined with *"chemotherapy," "pediatric,"* and *"acute lymphoblastic leukemia," "pediatric ALL,"* or *"childhood ALL."* Additional terms related to treatment phases, such as *"induction phase," "consolidation phase," "maintenance phase,"* and *"post-chemotherapy,"* were incorporated to capture phase-specific hematopoietic changes.

Study selection was restricted to original research articles reporting primary data on chemotherapy-induced hematopoietic suppression or recovery in children with ALL. Titles and abstracts were screened for relevance, followed by full-text evaluation of eligible studies. Methodological quality and relevance were assessed based on study design, sample size, outcome measures, and clarity of data presentation to ensure inclusion of studies with sufficient scientific rigor.

Studies were considered eligible for inclusion in this systematic review if they met several predefined criteria. Eligible articles were original research studies published between 2020 and 2025 and written in the English language. Only studies that were freely accessible in full text were included to ensure comprehensive data extraction and appraisal. In addition, studies were required to report hematopoietic effects of chemotherapy either before treatment, after treatment, or both in pediatric patients diagnosed with acute lymphoblastic leukemia (ALL).

Studies were excluded if they did not specifically evaluate the hematopoietic effects of chemotherapy in pediatric ALL populations. Review articles, systematic reviews, meta-analyses, case reports, editorials, and other forms of non-original research were also excluded. Furthermore, studies that were not available as full-text articles or were published in languages other than English were not considered eligible for inclusion.

Review Procedure

The review process followed several sequential steps: (1) identification of articles through database searches, (2) removal of duplicates, (3) screening based on titles and abstracts, (4) full-text review for eligibility, and (5) final inclusion and data extraction for synthesis. All steps adhered to the PRISMA 2020 flow diagram for transparency and reproducibility.

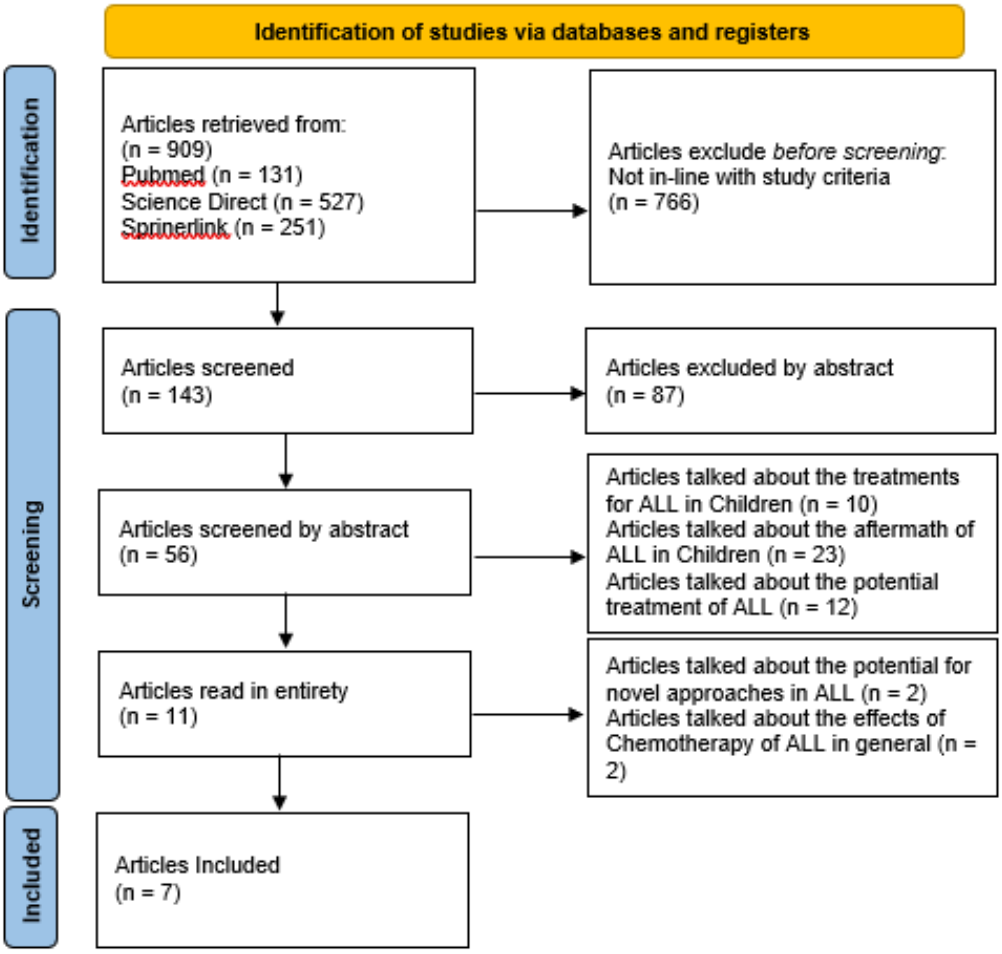

Figure 1. PRIMA Flowchart

RESULT AND DISCUSSION

A comprehensive literature search was conducted in PubMed, ScienceDirect, and SpringerLink, yielding a total of 909 records. After the removal of duplicate and clearly irrelevant articles, the remaining studies were screened based on their titles and abstracts in accordance with the predefined eligibility criteria.

Studies that did not evaluate chemotherapy related hematopoietic outcomes in pediatric ALL were excluded. Full-text assessment was subsequently performed for potentially eligible articles. Ultimately, 7 studies met the inclusion criteria and were included in the final qualitative synthesis. The study selection process is summarized in Figure 1.

A total of seven studies met the predefined eligibility criteria and were included in this systematic review. All included studies were conducted in pediatric populations with ALL receiving chemotherapy and evaluated hematopoietic alterations using peripheral blood parameters, bone marrow morphology, immunophenotyping, or combinations thereof. The study designs consisted of prospective observational studies (n = 3), retrospective cohort studies (n = 2), descriptive longitudinal studies (n = 1), and cross-sectional analytical studies (n = 1). The sample size ranged from

27 to 146 pediatric patients, with chemotherapy phases predominantly focused on induction therapy, although two studies extended observations into later treatment phases or post-therapy follow-up.

Table 1. Study Identification and Characteristics

No	Author	Country	Study Design	Sample	Chemotherapy Phase
1	Rashid Azeem et al. (2023)	Pakistan	Cross-sectional analytical	119 pediatric ALL patients	End of induction
2	Nguyen TV et al. (2015)	Australia	Prospective observational	44 pediatric ALL patients	Diagnosis, Day 15, End of induction
3	Grunnan JD & Rosthoj S. (2019)	Denmark	Retrospective cohort	66 pediatric ALL patients	Induction (5 weeks)
4	Rauf SE et al. (2016)	Turkey	Descriptive longitudinal	45 pediatric ALL patients	Induction
5	Xu Y et al. (2024)	China	Retrospective cohort	146 pediatric ALL patients	End of therapy, 6–12 months follow-up
6	Wicaksono S et al. (2024)	Indonesia	Prospective observational	27 pediatric ALL patients	Induction Phase (Week 1–6)
7	Park SH et al. (2019)	South Korea	Prospective serial bone marrow biopsy	29 pediatric ALL patients	Induction → delayed intensification

Hematopoietic Suppression During Induction Phase

The induction phase of chemotherapy in pediatric acute lymphoblastic leukemia represents the period of most profound hematopoietic suppression. This phase employs intensive multi-agent chemotherapy aimed at rapid leukemic blast eradication, which inevitably disrupts normal hematopoietic activity within the bone marrow. Across the included studies, induction therapy was consistently associated with marked suppression of erythropoiesis, granulopoiesis, and thrombopoiesis, as reflected by declines in hemoglobin levels, absolute neutrophil counts, and platelet counts[16,17].

Evidence from serial peripheral blood analyses demonstrated that hematopoietic suppression during induction was deep and sustained, with recovery occurring in a lineage-dependent and asynchronous manner. Reticulocyte counts and hemoglobin levels showed earlier signs of recovery, whereas neutrophil and platelet recovery occurred later, often extending beyond the completion of induction therapy. These findings indicate that clearance of leukemic blasts does not equate to immediate restoration of effective hematopoiesis[18].

Morphologic and immunohistochemical studies further support these observations by demonstrating that bone marrow cellular architecture and hematopoietic stem cell associated markers remain substantially altered during early treatment phases. Despite achievement of morphologic remission, normal hematopoietic elements and microenvironmental components exhibited delayed regeneration, highlighting the persistence of functional marrow impairment during induction chemotherapy[19]. These findings are consistent with recent pediatric ALL cohorts reporting induction therapy as the most myelotoxic phase of treatment

Collectively, these findings underscore that induction chemotherapy induces a phase of profound but heterogeneous hematopoietic suppression,

characterized by delayed recovery of marrow structure, stem cell compartments, and peripheral blood cell lineages. This prolonged disruption of hematopoiesis may contribute to clinical vulnerability during early treatment and emphasizes the need for careful monitoring of marrow recovery beyond blast clearance alone. From a clinical perspective, these observations support closer surveillance of hematopoietic recovery during induction, particularly through lineage-specific and early recovery markers, to better inform supportive care and treatment timing.

Table 2. Hematopoietic Parameters, Methods, and Outcomes

No.	Hematopoietic Parameters	Evaluation Method	Key Finding	Conclusion
1	Reticulocyte count	Manual & automated reticulocyte count + bone marrow cytology	Reticulocyte count correlated negatively with blast percentage and reflected marrow remission earlier than ANC	Reticulocyte count is a reliable surrogate marker of hematopoietic recovery
2	Bone marrow cellularity, fibrosis, stromal components	Morphometric analysis of trephine biopsy	Cellularity and fibrosis decreased during induction; adipocytes and megakaryocytes increased	Hematopoietic regeneration lags behind blast clearance
3	Hb, ANC, platelet, lymphocyte counts	Serial peripheral blood counts	Platelet recovery occurred earlier; neutrophil recovery was slowest	Hematopoietic recovery is asynchronous across lineages
4	Immature reticulocyte fraction (IRF), ANC	Automated hematology analyzer	IRF recovered significantly earlier than ANC	IRF is a sensitive early marker of marrow recovery
5	B cells, T cells, NK cells	Flow cytometry	B cells severely suppressed at end of therapy and recovered by 6 months; T-cell recovery delayed	Chemotherapy causes prolonged impairment of immune hematopoiesis
6	Hb, reticulocyte count, ANC, platelet count, IPF	Serial CBC and platelet indices	Erythropoiesis recovered earlier than granulopoiesis and thrombopoiesis	Hematopoietic recovery follows lineage-specific kinetics
7	CD34, CD133, CD117, CXCL12, CXCR4	Serial bone marrow immunohistochemistry	HSC and niche markers recovered sequentially across chemotherapy phases	True hematopoietic recovery extends beyond morphologic remission

Dynamic and Phase-Specific Recovery Patterns

Despite the profound myelosuppression observed during the induction phase, evidence from the included studies indicates that hematopoietic recovery progressively emerges during subsequent phases of chemotherapy. Importantly, this recovery is neither uniform nor synchronous across hematopoietic compartments, but instead follows a dynamic, phase-specific pattern. Bone marrow based investigations using serial immunohistochemical analyses demonstrated that regeneration of hematopoietic stem and progenitor cell populations occurs in close temporal association with reconstruction of the bone marrow microenvironment[20]. This phase-dependent pattern of recovery is consistent with recent bone marrow focused studies highlighting delayed niche restoration relative to stem and progenitor cell recovery.

Markers of hematopoietic stem cells, including CD133, CD34, and CD117, showed partial recovery during consolidation and interim maintenance, with more pronounced restoration observed between BM3 and BM5. In contrast, stromal and niche-related components of the marrow microenvironment, such as osteopontin and CXCL12, exhibited delayed recovery, reaching peak expression during later phases between BM5 and BM7. These findings indicate that post-chemotherapy bone marrow regeneration is a multistep process requiring coordinated restoration of both stem cell compartments and their supporting niche[21,22].

Prospective and observational clinical studies further support the dynamic and lineage-dependent nature of hematopoietic recovery at the peripheral blood level. Serial hematologic assessments consistently demonstrated that erythropoietic recovery precedes granulopoietic and thrombopoietic recovery during post-induction phases. Increases in reticulocyte counts were observed earlier than normalization of platelet counts and absolute neutrophil counts (ANC), while elevations in the immature platelet fraction (IPF) and reticulocyte indices occurred before recovery of mature platelet counts, suggesting their utility as sensitive early indicators of marrow regenerative activity[23]. Similar lineage-specific recovery kinetics have been reported in recent pediatric cohorts, reinforcing the value of early hematopoietic markers in monitoring post-induction marrow recovery.

The clinical implications of these recovery patterns are substantial. Early identification of hematopoietic regeneration using reticulocyte indices and IPF may allow clinicians to anticipate marrow reconstitution before conventional blood counts recover, thereby informing transfusion strategies and supporting more judicious use of hematopoietic growth factors. Within the included studies, IPF showed a consistent association with subsequent platelet recovery, reinforcing its value as a reliable marker of thrombopoietic activity during hematopoietic regeneration in pediatric patients receiving chemotherapy[24].

Bone Marrow Cellularity and Correlation with Peripheral Blood Counts

Histopathological assessment of bone marrow provides critical complementary information to peripheral blood measurements when evaluating hematopoietic recovery following chemotherapy. Several studies included in this review demonstrated a clear association between bone marrow cellularity and peripheral hematologic parameters at the end of the induction phase, typically around day 28. Reductions in marrow cellularity were consistently accompanied by decreases in hemoglobin levels, white blood cell counts, and platelet counts, reflecting ongoing suppression of normal hematopoiesis [16,19]. These findings are in line with recent marrow-based studies reporting that peripheral cytopenias during early post-induction phases closely parallel underlying reductions in marrow cellularity.

Although effective leukemic blast clearance was achieved in most patients at the completion of induction therapy, a proportion of patients exhibited persistent marrow hypocellularity and impaired erythropoiesis. These findings indicate that restoration of normal hematopoietic function does not occur concurrently with blast eradication and instead follows a delayed and phased recovery process. Consequently, normalization or partial recovery of peripheral blood counts may not accurately reflect the underlying status of bone marrow regeneration, particularly during early post-induction periods [23,25]. Similar discordance between peripheral blood recovery and marrow regeneration has been described in recent studies, emphasizing that peripheral counts alone may provide a false sense of hematopoietic recovery.

Evidence from morphologic and immunohistochemical studies further underscores the limitations of relying solely on peripheral blood indices to assess marrow recovery. Persistent alterations in marrow cellular architecture and delayed regeneration of hematopoietic compartments have been observed despite apparent hematologic improvement. An integrated evaluation combining bone marrow assessment with peripheral blood parameters may therefore provide a more accurate representation of hematopoietic recovery. Such an approach has potential clinical relevance for optimizing the timing of subsequent chemotherapy phases, avoiding overtreatment during incomplete marrow recovery, and individualizing supportive care strategies in pediatric patients with acute lymphoblastic leukemia[18,26]. From a clinical standpoint, integrating marrow and peripheral blood assessments may improve risk stratification and treatment decision-making during early phases of therapy.

CONCLUSION

This systematic review shows that chemotherapy in pediatric acute lymphoblastic leukemia causes profound but heterogeneous hematopoietic suppression, particularly during the induction phase. Hematopoietic recovery occurs in a dynamic, phase-specific, and lineage-dependent manner, with asynchronous restoration of erythropoiesis, granulopoiesis, and thrombopoiesis. Notably, morphologic remission does not necessarily reflect immediate functional recovery of hematopoiesis. Bone marrow–based findings further demonstrate delayed recovery of hematopoietic stem cell compartments and the marrow microenvironment in a subset of patients, highlighting the limitations of relying solely on peripheral blood counts. Clinically, integrated assessment using peripheral blood parameters, early recovery markers such as reticulocyte indices and immature platelet fraction, and selective bone marrow evaluation may improve monitoring of hematopoietic recovery and guide supportive care during therapy. Further prospective studies are needed to refine hematopoietic monitoring strategies in pediatric acute lymphoblastic leukemia.

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