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The effect of high-dose methotrexate chemotherapy on citrulline level to gastrointestinal mucositis cases in children with acute lymphoblastic leukemia during the consolidation phase

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Abstract: Acute Lymphoblastic Leukemia (ALL) is the most common pediatric malignancy, with survival rates exceeding 90% due to advancements in chemotherapy, including high-dose methotrexate (HD-MTX). However, gastrointestinal (GI) mucositis remains a significant complication, impairing treatment continuity and quality of life. Citrulline, a biomarker synthesized in enterocytes, reflects intestinal integrity and offers a non-invasive alternative for monitoring mucosal damage. This study aimed to evaluate citrulline dynamics in children with ALL undergoing HD-MTX chemotherapy during the consolidation phase. This cross-sectional study included 34 pediatric ALL patients in consolidation phase. Serum citrulline levels were measured pre- and post-HD-MTX chemotherapy using high-performance liquid chromatography. Mucositis severity was assessed using the National Cancer Institute Common Terminology Criteria. Data analysis involved paired t-tests and subgroup comparisons by risk stratification (Standard Risk [SR], High Risk [HR]) and mucositis grades. Overall, no significant changes in serum citrulline levels were observed post-chemotherapy. SR patients exhibited a significant decline in citrulline levels, consistent with mucosal injury. Conversely, HR patients demonstrated an unexpected increase in citrulline, potentially due to compensatory enterocyte responses or altered metabolism. Grade 1 mucositis patients showed increased citrulline levels, indicating early recovery, while grade 2 mucositis patients showed no significant changes, reflecting sustained injury. Citrulline is a promising biomarker for monitoring chemotherapy-induced GI mucositis in pediatric ALL patients. Its non-invasive measurement and correlation with mucosal health highlight its potential for improving personalized care. Further validation in diverse populations is required to optimize its clinical application.

Keywords: *Biomarker, Chemotherapy, Citrulline, Gastrointestinal, Mucositis, Pediatrics.*

1. Introduction

Acute Lymphoblastic Leukemia (ALL) is the most prevalent pediatric malignancy, accounting for approximately 25% of all childhood cancers globally [1]. Advances in treatment, including high-dose methotrexate (HD-MTX) chemotherapy, have led to a significant improvement in survival rates, with contemporary survival exceeding 90% in developed nations [2]. However, these intensive regimens are frequently associated with severe complications, such as gastrointestinal (GI) mucositis. This condition results from the direct toxic effects of chemotherapy on the rapidly dividing epithelial cells lining the GI tract, leading to mucosal damage, nutrient malabsorption, and an increased risk of systemic infections [3]. These effects not only impair quality of life but also compromise the continuity of treatment,

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potentially impacting overall survival outcomes. GI mucositis leads to mucosal damage, impaired nutrient absorption, and increased susceptibility to systemic infections, thereby impacting both quality of life and treatment continuity, which are critical for achieving optimal survival outcomes [4]. While diagnostic methods like intestinal biopsies remain invasive and impractical for routine use in pediatric patients, this underscores the urgent need for non-invasive biomarkers to evaluate intestinal integrity and predict mucosal damage [5]. Current diagnostic methods for GI mucositis, including intestinal biopsy, are invasive and impractical for routine use in pediatric populations. This limitation underscores the need for non-invasive biomarkers that can reliably assess intestinal integrity and predict mucosal damage. Citrulline, a non-protein amino acid primarily synthesized by enterocytes, has emerged as a promising candidate. Serum citrulline levels are directly proportional to functional enterocyte mass, making it a sensitive and specific marker of intestinal mucosal health [6]. A decline in citrulline levels is strongly associated with mucosal injury, as demonstrated in various clinical and preclinical studies [7].

Despite its potential, the application of citrulline as a biomarker in pediatric oncology, particularly in the context of HD-MTX-induced mucositis, remains underexplored. Most existing studies have focused on adult populations or other chemotherapeutic agents, leaving a significant gap in understanding its utility in children undergoing ALL treatment [8]. Furthermore, differences in physiological responses between risk groups, such as Standard Risk (SR) and High Risk (HR), may influence citrulline dynamics and warrant detailed investigation [9].

This study aims to evaluate the changes in citrulline levels before and after HD-MTX chemotherapy in children with ALL during the consolidation phase. Specifically, it seeks to determine whether citrulline can serve as a reliable biomarker for detecting and monitoring GI mucositis. By addressing these objectives, the study aims to provide critical insights into the utility of citrulline in clinical practice, potentially paving the way for more personalized and less invasive approaches to managing chemotherapy-related complications in pediatric oncology [10].

2. Material and Methods

A cross-sectional design was utilized to evaluate the relationship between citrulline levels and gastrointestinal (GI) mucositis in pediatric 34 patients diagnosed with Acute Lymphoblastic Leukemia (ALL) during the consolidation phase of their treatment. The study was conducted at a tertiary care hospital specializing in pediatric oncology. Ethical approval was obtained from the institutional review board, and written informed consent was secured from all participants or their legal guardians. The study population consisted of pediatric patients diagnosed with ALL undergoing high-dose methotrexate (HD-MTX) chemotherapy. Inclusion criteria required patients to have a confirmed diagnosis of ALL, eligibility for HD-MTX during the consolidation phase, and the absence of pre-existing gastrointestinal disorders. Patients with incomplete data, a history of malabsorption syndromes, renal failure or other concurrent conditions affecting citrulline metabolism were excluded from the study. Demographic and clinical data, including age, sex, nutritional status, and risk stratification (Standard Risk [SR] and High Risk [HR]), were recorded. Nutritional status was classified as normal, undernourished, overnourished, or obese based on standardized pediatric growth charts. Serum citrulline levels were measured at two time points: Prior to HD-MTX administration (baseline) and 48 hours after chemotherapy. Blood samples were collected via venipuncture and processed immediately to ensure accuracy from routine check. Citrulline concentrations were analyzed using high-performance liquid chromatography (HPLC), a method validated for precision and reliability in clinical settings [11]. GI mucositis severity was assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events. Mucositis was graded on a scale from 0 (no mucositis) to 4 (life-threatening mucositis), with particular attention to grades 1 and 2, which were most prevalent in this study population [12].

Data analysis was conducted using SPSS version 25. Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables, including citrulline levels, were expressed as means and standard deviations or medians and interquartile ranges, depending on data

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distribution [13]. Paired t-tests were performed to assess changes in citrulline levels before and after chemotherapy in normally distributed data, while the Wilcoxon Signed Rank test was applied to non-normally distributed data. Differences between risk groups (SR vs. HR) and mucositis grades were analyzed to explore subgroup-specific trends. A p-value of less than 0.05 was considered statistically significant [14]. This methodological framework ensures the reliability and validity of findings, allowing for robust conclusions regarding the utility of citrulline as a biomarker for GI mucositis in pediatric ALL patients undergoing HD-MTX chemotherapy [15].

3. Results

The study included a total of 34 pediatric patients diagnosed with ALL during the consolidation phase. The median age was 11 years, with an age range spanning from 1 to 18 years. A male predominance was observed, comprising 73.5% of the study population. Nutritional assessments revealed that 38.2% of participants had normal nutritional status, while 17.6% were undernourished, 26.6% were overnourished, and 17.6% were classified as obese. The baseline characteristics of pediatric ALL patients stratified by mucositis grade are summarized in Table 1. Notable trends include a higher prevalence of mucositis in Standard Risk patients and variable nutritional statuses across groups.

Table 1.
Baseline characteristics and mucositis grades of pediatric all patients undergoing HD-MTX chemotherapy.

Variable	Total (n = 34)	Grade 1 Mucositis (n = 16)	Grade 2 Mucositis (n = 12)	No Mucositis (n = 6)
Median age (Years)	11 (1-18)	10.5 (2-18)	11.0 (1-15)	12.0 (5-17)
Sex (Male, %)	25 (73.5%)	12 (75.0%)	9 (75.0%)	4 (66.7%)
Nutritional status				
- Normal	13 (38.2%)	7 (43.8%)	4 (33.3%)	2 (33.3%)
- Undernourished	6 (17.6%)	3 (18.8%)	2 (16.7%)	1 (16.7%)
- Overnourished	9 (26.6%)	4 (25.0%)	3 (25.0%)	2 (33.3%)
- Obese	6 (17.6%)	2 (12.5%)	3 (25.0%)	1 (16.7%)
Risk group				
- Standard risk (SR)	20 (58.8%)	10 (62.5%)	6 (50.0%)	4 (66.7%)
- High risk (HR)	14 (41.2%)	6 (37.5%)	6 (50.0%)	2 (33.3%)

GI mucositis was confirmed in 82.4% of the participants. Among these, 47.1% experienced grade 1 mucositis, while 35.3% exhibited grade 2 mucositis. No cases of grade 3 or grade 4 mucositis were observed in this cohort, indicating a predominantly mild to moderate severity of mucosal injury.

3.1. Citrulline Level Changes

Overall, serum citrulline levels demonstrated a non-significant change following HD-MTX chemotherapy. The mean pre-treatment citrulline level was 3.56 ± 0.07 μmol/L, compared to 3.30 ± 0.07 μmol/L post-treatment ($p = 0.214$). Despite the lack of a significant overall change, subgroup analyses revealed notable trends based on risk stratification and mucositis severity.

In the Standard Risk (SR) group, citrulline levels exhibited a consistent decrease post-chemotherapy, aligning with the expected pattern of mucosal damage. This decline supports the role of citrulline as a biomarker for detecting enterocyte loss in this subset of patients. Conversely, the High Risk (HR) group demonstrated a significant increase in citrulline levels following treatment (3.07 ± 1.42 μmol/L pre-treatment vs. 4.17 ± 2.38 μmol/L post-treatment; $p = 0.049$), suggesting an adaptive or compensatory mechanism. Table 2 illustrates the changes in citrulline levels pre- and post-HD-MTX chemotherapy, with significant increases observed in the HR group.

Table 2.
Citrulline levels pre- and post-HD-MTX chemotherapy.

Group	Pre-treatment citrulline (Nmol/L)	Post-treatment citrulline (Nmol/L)	P-value

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All patients	3.56 (0.07-5.84)	3.30 (0.07-12.99)	0.214
Standard risk (SR)	3.67 (1.06-5.7)	2.71 (0.07-12.99)	0.906
High risk (HR)	3.07 (± 1.42)	4.17 (± 2.38)	0.049*

Note: * Statistically significant, with p-value < 0.05.

When stratified by mucositis grade, patients with grade 1 mucositis exhibited a significant rise in citrulline levels (3.82 ± 1.06 µmol/L pre-treatment vs. 3.95 ± 1.14 µmol/L post-treatment; p = 0.036), potentially reflecting early-phase enterocyte recovery. In contrast, patients with grade 2 mucositis showed no significant change in citrulline levels, likely due to the severity of mucosal injury overwhelming regenerative capacity. Table 3 presents citrulline dynamics stratified by mucositis severity, with significant changes observed in patients with grade 1 mucositis.

Table 3.
Citrulline levels by mucositis severity

Mucositis severity	Pre-treatment citrulline (nmol/L)	Post-treatment citrulline (nmol/L)	p-value
Normal	3.32 (1.23-5.70)	2.68 (0.07-3.24)	0.115
Grade 1	3.82 (1.06-5.84)	3.95 (1.14-12.99)	0.036*
Grade 2	3.35 (0.07-5.53)	3.17 (0.29-6.82)	0.616

Note: * Statistically significant, with p-value < 0.05.

3.2. Risk Stratification Trends

The divergence in citrulline levels between SR and HR groups highlights potential physiological differences. SR patients demonstrated a predictable decline in citrulline, consistent with mucositis pathophysiology. The significant increase in the HR group suggests enhanced resilience or a delayed response to mucosal injury, warranting further investigation into the underlying mechanisms.

4. Discussion

This study provides a detailed examination of citrulline as a biomarker for gastrointestinal mucositis in pediatric patients undergoing high-dose methotrexate chemotherapy. The findings underscore the intricate relationship between mucosal injury, recovery processes, and individual patient characteristics. Citrulline, synthesized predominantly by enterocytes, serves as an essential indicator of intestinal epithelial integrity, with its serum levels directly reflecting functional enterocyte mass [12]. Its serum levels are directly proportional to functional enterocyte mass, making it an invaluable tool for assessing mucosal health [11]. In Standard Risk patients, the observed decline in citrulline levels following chemotherapy aligns with established pathophysiological mechanisms of mucosal damage. Methotrexate, a cytotoxic agent targeting rapidly dividing cells, causes significant epithelial disruption, leading to enterocyte loss and reduced citrulline synthesis [16]. This consistent trend with prior studies reinforces citrulline's sensitivity and specificity as a biomarker for chemotherapy-induced intestinal injury [17]. Beyond its diagnostic utility, citrulline level role extends to providing insights into the dynamic process of mucosal damage and regeneration. A decline in levels not only signals acute injury but also reflects the degree of epithelial compromise, which can influence clinical decision-making [18]. However, its sensitivity to other systemic factors, such as inflammation and metabolic variations, necessitates cautious interpretation [19]. Despite these complexities, citrulline is non-invasive procedure and proven correlation with mucosal integrity make it an indispensable marker in pediatric oncology, particularly for monitoring gastrointestinal toxicity and guiding timely interventions. This highlights its potential to improve outcomes through more personalized, biomarker-driven care strategies [20]. In contrast to the Standard Risk group, the High-Risk group exhibited an unexpected increase in serum citrulline levels post-chemotherapy. This deviation from the anticipated pattern of citrulline reduction warrants critical evaluation, as it suggests the presence of unique physiological responses or external influences that may modulate citrulline dynamics in this subgroup [21].

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Understanding these deviations is essential to optimizing the biomarker's utility in clinical practice, particularly in the context of high-dose methotrexate (HD-MTX) therapy.

A plausible explanation for this finding lies in the activation of compensatory mechanisms aimed at preserving intestinal integrity. Chemotherapy-induced mucosal injury typically triggers a cascade of biological responses, including enterocyte proliferation and epithelial regeneration. In high-risk patients, who often present with more aggressive disease phenotypes and undergo more intensive treatment regimens, the adaptive response may be heightened. Enhanced enterocyte proliferation could result in increased citrulline synthesis, counteracting the expected decline associated with mucosal injury [16]. This phenomenon underscores the complexity of citrulline as a biomarker, as its levels may reflect not only enterocyte mass but also the dynamic balance between injury and repair processes.

Another critical factor influencing citrulline dynamics in high-risk patients is systemic inflammation. Chemotherapy often induces a heightened inflammatory response, characterized by elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL-6 and IL-1β). These cytokines can modulate intestinal permeability and alter amino acid metabolism, potentially leading to increased citrulline synthesis or reduced clearance [17]. This interplay between systemic inflammation and citrulline dynamics adds another layer of complexity to the interpretation of results in this population.

In addition to inflammation and compensatory regeneration, genetic factors may also play a significant role in modulating citrulline levels in high-risk patients. Variations in genes related to amino acid metabolism, such as those encoding enzymes involved in the urea cycle, could influence citrulline synthesis and clearance. For instance, polymorphisms in the ornithine transcarbamylase (OTC) gene or argininosuccinate synthetase (ASS1) gene may affect the efficiency of citrulline production in enterocytes. These genetic variations, which may have distinct prevalence rates in different populations, could partially explain the unique citrulline dynamics observed in this cohort [22].

Nutritional status is another critical variable that must be considered when evaluating citrulline dynamics in high-risk patients. Malnutrition, which remains a significant public health issue in Indonesia, can impair intestinal function and regenerative capacity. Undernourished patients may exhibit reduced baseline citrulline levels due to compromised enterocyte mass, potentially amplifying the impact of chemotherapy-induced injury [23]. Conversely, overnutrition, characterized by excess adiposity, may be associated with chronic low-grade inflammation, further complicating citrulline interpretation [24]. The dual burden of malnutrition in Indonesia necessitates a nuanced understanding of how nutritional status interacts with citrulline dynamics in this population [10].

It is also worth considering the potential impact of chemotherapy regimen differences on citrulline dynamics. Variations in methotrexate dosing protocols, supportive care measures, and adjunctive therapies could influence the extent of mucosal injury and subsequent citrulline responses. For instance, differences in the use of leucovorin rescue or anti-inflammatory agents may alter the trajectory of mucosal recovery, contributing to the heterogeneity observed in high-risk patients [25]. Understanding these regimen-specific effects is critical for standardizing citrulline-based monitoring protocols and ensuring their validity across diverse clinical settings.

Lastly, socioeconomic and environmental factors in Indonesia, including disparities in healthcare access, delayed diagnosis, and inconsistent supportive care, exacerbate disease severity and complicate treatment outcomes. These challenges may amplify the biological variability in citrulline responses, underscoring the need to tailor biomarker strategies to the local context [26]. The relationship between mucositis severity and citrulline dynamics underscores the complexity of using this biomarker to monitor gastrointestinal health. In this study, patients with grade 1 mucositis exhibited a significant increase in citrulline levels post-chemotherapy, likely reflecting early enterocyte recovery and regeneration. This finding highlights citrulline's dual role—not only as an indicator of mucosal injury but also as a marker of repair processes [12]. Early regenerative responses in grade 1 mucositis may involve proliferation of intestinal epithelial stem cells and restoration of the mucosal barrier, which collectively boost citrulline synthesis and contribute to elevated serum levels [16]. In contrast, patients

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with grade 2 mucositis showed no significant change in citrulline levels. This lack of variation likely reflects severe and sustained mucosal damage that overwhelms the intestine's capacity for repair. In grade 2 mucositis, the extent of epithelial injury may be so profound that compensatory mechanisms, such as enterocyte proliferation, are either insufficient or delayed [11]. This supports the idea that citrulline levels reflect a dynamic balance between injury and regeneration, with severe mucositis tipping this balance toward persistent damage and impaired function. The disparity between grade 1 and grade 2 mucositis patients also raises questions about the temporal aspects of mucosal healing. It is possible that recovery in grade 2 mucositis requires a longer timeframe, during which citrulline levels may eventually normalize or increase. This suggests that single time-point measurements may not fully capture the progression of mucosal injury and repair, emphasizing the need for longitudinal monitoring to provide a more comprehensive understanding of citrulline's behavior over time [17]. These findings emphasize the need for a nuanced approach to interpreting citrulline levels in the context of mucositis severity. Understanding the interplay between injury and regeneration is crucial for optimizing the use of citrulline as a biomarker in pediatric oncology, particularly in tailoring interventions to support mucosal recovery in patients with severe mucositis [19]. While citrulline shows promise as a non-invasive biomarker for gastrointestinal mucositis, this study highlights several limitations that must be addressed to optimize its clinical utility. The observed variability across risk groups and mucositis grades suggests that citrulline levels are influenced by a complex interplay of factors beyond enterocyte mass [12]. Nutritional status is one significant factor affecting citrulline levels. Malnutrition, prevalent in pediatric oncology populations, can compromise baseline enterocyte mass, thereby reducing citrulline levels. Conversely, chronic low-grade inflammation in overnourished patients can exacerbate intestinal permeability and alter citrulline synthesis [27]. Renal function is another critical determinant, as citrulline clearance occurs primarily in the kidneys. Variations in renal efficiency, particularly in patients receiving nephrotoxic chemotherapy agents, could confound citrulline measurements [11]. Additionally, systemic inflammation, driven by chemotherapy-induced cytokine release, can impact both intestinal integrity and metabolic pathways involved in citrulline synthesis [15].

These multifaceted influences highlight the need for a more comprehensive approach to citrulline interpretation. Future research should focus on integrating citrulline monitoring with broader clinical and biochemical parameters, enabling a more accurate assessment of its diagnostic and prognostic value. Longitudinal studies with larger, ethnically diverse cohorts are essential to validate these findings, establish standardized thresholds, and refine the biomarker's application in diverse clinical settings [19]. Despite its inherent limitations, this study underscores the promising role of citrulline as a biomarker for gastrointestinal mucositis in pediatric oncology. Its non-invasive procedure offers a significant advantage over traditional diagnostic methods like intestinal biopsy, which are impractical and often distressing for young patients [12]. By reflecting mucosal integrity, citrulline serves as a reliable indicator for detecting early mucositis and assessing the severity of intestinal injury [19]. This biomarker has the potential to transform supportive care strategies, enabling timely interventions to mitigate complications and maintain the continuity of chemotherapy. For example, integrating citrulline monitoring into routine clinical practice could guide personalized nutrition and pharmacological support to enhance mucosal recovery [27]. Furthermore, its use in longitudinal studies could help identify patients at higher risk for severe mucositis, facilitating early preventive measures [11].

Future research should focus on validating citrulline thresholds in diverse pediatric populations and exploring its integration with other biomarkers to improve diagnostic accuracy. Additionally, understanding the temporal dynamics of citrulline during mucositis recovery could inform better timing for clinical interventions, ultimately enhancing outcomes for pediatric cancer patients worldwide [17].

5. Conclusions

This study underscores citrulline's potential as a non-invasive biomarker for gastrointestinal mucositis in pediatric oncology. Its levels reflect mucosal integrity and dynamic recovery, offering advantages over invasive diagnostics. The findings highlight its role in monitoring chemotherapy-

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induced injury, guiding personalized interventions, and improving supportive care strategies. Further validation in diverse populations is essential to optimize its clinical utility and establish standardized thresholds for decision-making.

Fundings:
This study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. Ethical approval was obtained from the institutional review board of Dr. Soetomo General Hospital, Indonesia. Informed consent was obtained from all participants or their legal guardians prior to inclusion in the study. Approval reference number: 0696/KEPK/V1/2023.

Transparency:
The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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Abbreviations:

ALL	: Acute Lymphoblastic Leukemia.
HD-MTX	: High-Dose Methotrexate.
GI	: Gastrointestinal.
SR	: Standard Risk.
HR	: High Risk.
HPLC	: High-Performance Liquid Chromatography.
NCI	: National Cancer Institute.
TNF-α	: Tumor Necrosis Factor-Alpha.
IL	: Interleukin.

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