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RESEARCH ARTICLE

Use of Oral Metformin Therapy for Therapy-Induced Hyperglycemia in Pediatric Patients With Acute Lymphoblastic Leukemia

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ABSTRACT

Background: Hyperglycemia during treatment for pediatric acute lymphoblastic leukemia (ALL) is often induced by corticosteroids and asparaginase. Although insulin remains the standard therapy, oral metformin presents a promising alternative due to its ease of use, lower risk of hypoglycemia, and noninvasive route of administration—factors that can significantly enhance patient comfort and quality of life.

Objective: To evaluate the efficacy and safety of oral metformin in managing therapy-induced hyperglycemia (TIH) in children with ALL.

Materials and Methods: An ambispective analysis was conducted over 6 years (September 2018–August 2024) in pediatric ALL patients who developed hyperglycemia during induction or re-induction. We assessed the effectiveness of metformin in controlling hyperglycemia and the need for insulin in cases of suboptimal response.

Results: Out of 281 ALL patients, 54 (19.2%) developed TIH, with a median age of 12 years (range 5–16). Most cases (57.4%, $n = 31$) occurred in the preadolescent/adolescent group. Pre-B ALL accounted for 85.2% ($n = 46$), and T-ALL for 14.8% ($n = 8$). A WBC count $>20 \times 10^9$/L was noted in 44.4% ($n = 24$). BMI was normal in 63% ($n = 34$), whereas 22.2% ($n = 12$) were overweight. Extremes of BMI (underweight/obese) were seen in 7.4% ($n = 4$) each. Most cases occurred during induction (49 patients), with 17 experiencing recurrence during re-induction. Hyperglycemia typically appeared within a week of initiating steroids. The mean baseline glucose was 240 mg/dL (range: 201–338 mg/dL), which declined to 137 mg/dL at Day 7 (range: 110–174 mg/dL), with a mean reduction from baseline of 103 mg/dL. Metformin (up to 1500 mg/day) successfully controlled blood glucose in 36 induction-phase patients (73.4%, 95% CI 59.7–83.8), whereas 13 (26.5%) required insulin. During re-induction, seven patients needed dual therapy. Insulin was added for glucose >300 mg/dL, signs of ketoacidosis, or poor response to metformin. In the TIH group, febrile neutropenia and culture-positive sepsis occurred in 42.6% ($n = 23$) and 24.1% ($n = 13$), respectively—higher than in non-hyperglycemic patients. All patients reverted to euglycemia after steroid tapering, with no long-term hypoglycemic therapy needed. Metformin was well-tolerated, with no adverse effects warranting discontinuation. Glycemic management did not interfere with leukemia remission or treatment completion.

Abbreviations: ALL, acute lymphoblastic leukemia; AVN, avascular necrosis; POC, point of care; TIH, therapy-induced hyperglycemia; TRM, treatment-related mortality.

Conclusion: Oral metformin proved to be a safe and effective first-line option for managing TIH in pediatric ALL. Insulin therapy could be avoided in majority of the patients (73.4% in induction, 68.1% in re-induction), making this drug an attractive first-line option for children with treatment-induced non-severe hyperglycemia.

1 | Introduction

Therapy in pediatric acute lymphoblastic leukemia (ALL) can be complicated by hyperglycemia, the estimated prevalence of which varies between 9.7% and 69% [1]. It is often associated with chemotherapeutic agents altering glycemic control, particularly glucocorticoids and asparaginase. Early recognition and prompt management of hyperglycemia is important in childhood cancer therapy, as it can otherwise be associated with an increased risk of infections and morbidity. Published literature or consensus regarding glycemic patterns and case-based management of hyperglycemia during treatment for childhood cancer is lacking.

Traditionally, insulin therapy has been used for the treatment of symptomatic hyperglycemia in patients with ALL. Insulin requires subcutaneous administration and frequent monitoring of the blood glucose (BG) level to prevent hypoglycemia. Subcutaneous injections and finger pricks for glucose monitoring required with insulin therapy may add more discomfort and stress to the child and family. Metformin, a biguanide and an oral antidiabetic agent is not often associated with hypoglycemia. There is limited literature on the use of metformin or other oral antidiabetic agents in pediatric patients with cancer [2]. We intend to review the outcomes of glycemic control in children with ALL who were started on metformin in response to therapy-induced hyperglycemia (TIH).

2 | Materials and Methods

Patients with ALL who underwent treatment in our hospital over 6 years from September 2018 to August 2024 and developed hyperglycemia were studied in an ambispective manner. The criteria for diagnosis of hyperglycemia were a marked elevation of the BG, including a random BG concentration ≥11.1 mmol/L (200 mg/dL) or fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL) in the presence of overt symptoms [3]. Urine test for ketones was done if patient presented with symptoms of hyperglycemia or ketoacidosis. Metformin was started at a dose ranging from 250 to 500 mg/day with weekly 500 mg increments as tolerated up to a maximum of 1000 mg twice daily or 850 mg thrice daily (or 2000 mg/day once in the case of extended release tablets). Insulin therapy was started upfront at random BG levels of >300 mg/dL or added as a second agent if optimal glycemic control could not be achieved at a dose of 1500 mg of metformin. Parents were trained regarding home glucose monitoring with the help of bedside point-of-care (POC) capillary glucose monitoring and report to the team via a helpline assistance number. Patients and their caregivers were also counseled about lifestyle and dietary modifications and other appropriate conservative measures.

2.1 | Statistical Analysis

Statistical analysis was performed using SPSS version 23 (IBM Corp.). Descriptive statistics were used to summarize patient demographics and clinical characteristics. Continuous variables were reported as mean with standard deviation (SD) or median with range, as appropriate for their distribution, whereas categorical data were presented as frequencies and percentages. The primary analysis of treatment efficacy involved assessing longitudinal changes in glucose levels within various clinical subgroups; these repeated-measures comparisons were conducted using the nonparametric Friedman test. For comparisons of continuous outcomes between two independent groups (e.g., insulin vs. metformin monotherapy, or by steroid type), the Wilcoxon–Mann–Whitney test was used. The Kruskal–Wallis test was applied for comparisons across three or more age groups. To model and compare the overall glucose reduction trajectories over multiple timepoints between different subgroups, generalized estimating equations (GEE) were employed. A p value of <0.05 was considered statistically significant for all analyses.

3 | Results

3.1 | Clinical Characteristics and Leukemia Therapy

During the period of the study, 281 patients with ALL were treated in our hospital, of which 54 developed hyperglycemia. Thus, the prevalence of hyperglycemia among leukemia patients in our hospital was 19.2%. Of this, majority (70.4%, $n = 38$) were males, with M:F ratio being 2.5:1. The median age was 12 years (range 5–16 years) with 31 patients (57.4%) being in the adolescent age group. The majority of them were cases of pre-B ALL (85.2%, $n = 46$), whereas T-ALL comprised the remainder of the cases. A WBC count of $\geq 20 \times 10^9/\text{L}/\text{mm}^3$ was seen in 44.4% ($n = 24$) of our patients, of which nearly half (58.3%, $n = 14/54$) had hyperleukocytosis (WBC count $>50 \times 10^9/\text{L}/\text{mm}^3$); however, it was not statistically significant ($p = 0.08$) as a risk factor for hyperglycemia. The median WBC count was $16.5 \times 10^9/\text{L}$. A normal BMI was seen in 63.0% ($n = 34$), whereas 22.2% ($n = 12$) of the children were overweight, whereas the extremes (underweight and obesity) comprised 7.4% ($n = 4$) each. Prednisolone was used for induction therapy in B-ALL patients, whereas children with T-ALL received dexamethasone. Majority (90.7%, $n = 49$) of patients developed hyperglycemia during induction therapy, with only five patients showing elevated BG for the first time during re-induction. Of the 49 cases, 17 patients developed recurrence of hyperglycemia during the re-induction phase of treatment. The duration of the first occurrence of hyperglycemia from the onset of starting steroids was within a week in the majority of the patients (66.6%; $n = 36$), by 2 weeks in 20.4% ($n = 11$), and as late as 3 weeks and beyond in 13.0% ($n = 7$). Ten of them (18.5%)

had a family history of diabetes (Type 2). One patient presented with features of ketoacidosis, which was successfully managed within 48 h of insulin administration. HbA1c was measured in 11 patients, with 5 showing elevated levels (>6.5%). C-peptide levels were tested in six patients, and low levels were observed in three. Three patients developed avascular necrosis (AVN) during active treatment, whereas two patients developed AVN during long-term follow-up, 1.5 years after completing treatment. Day 29 MRD positivity was observed in 4 of 54 patients with TIH (7.4%) and in 19 of 227 patients without TIH (8.3%), indicating no substantial difference between the two groups.

3.2 | Associated Metabolic Derangements

Twenty-six patients (48.1%) experienced hypertension alongside hyperglycemia, with six of them developing hypertension for the first time during re-induction therapy. Four patients were diagnosed with hypothyroidism during treatment, whereas three had documented hyperlipidemia, characterized by elevated triglyceride levels. Among these, two patients had both hyperlipidemia and hypertension, occurring simultaneously with TIH. These metabolic disturbances resolved by the end of the intensive treatment phase, with only one patient continuing oral thyroxine during the maintenance phase. None of the children with TIH had signs or symptoms of pancreatitis. However, the overall incidence of pancreatitis in our cohort was 3.7% ($n = 2$).

3.3 | Infections

Febrile neutropenia occurred in 23 (42.6%) of these patients with TIH. Among these, seven patients had Gram-negative sepsis, four had Gram-positive bacteremia, and fungal sepsis in two patients. One patient developed cerebral aspergillosis, whereas three of them developed pulmonary aspergillosis, all during the induction phase. Four patients with febrile neutropenia presented with neutropenic enterocolitis, and one showed symptoms of lower limb cellulitis. Seven of the febrile neutropenia patients required ICU admission, with two needing inotropic and oxygen support; however, all of them recovered with no treatment related mortality (TRM). Overall, in patients with TIH during ALL therapy, the incidence of febrile neutropenia and culture positive sepsis was 42.6% and 24.1%, respectively.

3.4 | Hyperglycemia Treatment

Metformin was started at a dose ranging from 250 to 500 mg/day with weekly 500 mg increments as tolerated up to a maximum of 1000 mg twice daily or 850 mg thrice daily (or 2000 mg/day once in the case of extended release tablets). Insulin therapy was initiated for patients with BG >300 mg/dL or added as a second agent if optimal glycemic control was not achieved with a dose of 1500 mg of metformin. Treatment was continued until after the corticosteroid therapy was completed. The mean baseline glucose was 240 mg/dL (range: 201–338 mg/dL), which declined to 137.91 mg/dL at Day 7 (range: 110–174 mg/dL), with a reduction from baseline of 103 mg/dL. The mean change in glucose levels in our patients from Day 1 to 7 has been shown in Figure 1. Metformin was successfully used at the first episode of TIH in 41 of 54 patients (76.0%; 95% CI 63.2–85.7). Among those with recurrent hyperglycemia during re-induction, metformin alone achieved glycemic control in 10 of 17 patients (58.8%; 95% CI 36.0–78.4).

Phase-wise, during induction, glycemic control was achieved with metformin monotherapy in 36 of 49 patients (73.4%; 95% CI 59.7–83.8), whereas 13 (26.5%) required the addition of insulin. During re-induction, 15 of 22 patients (68.1%; 95% CI 47.6–83.6) were managed with metformin alone, whereas 7 required combined therapy with metformin and an insulin analogue. Overall, these findings demonstrate that metformin monotherapy effectively controlled TIH in the majority of patients across both induction and re-induction phases and during first and recurrent hyperglycemic episodes. None of these patients developed long-term hyperglycemia after discontinuation of leukemia treatment.

4 | Discussion

Hyperglycemia is a recognized complication of induction chemotherapy in children with ALL. Hyperglycemia is most frequently observed during the induction phase of therapy, likely due to glucocorticoids and asparaginase. Corticosteroids contribute to hyperglycemia by damaging pancreatic beta cells, which reduces insulin production, increases insulin resistance, stimulates gluconeogenesis and lipolysis, and elevates counter-regulatory hormones like glucagon and adrenaline, and also promotes apoptosis of pancreatic beta cells. The type of corticosteroid used (dexamethasone vs. prednisolone) does not appear to influence the occurrence of TIH during ALL therapy. However, evidence suggests that both the dose and duration of corticosteroid administration can significantly impact the development of TIH [4]. The second offending agent L-asparaginase, depletes L-asparagine, which can lead to decreased insulin synthesis and secretion. It has also been shown to increase insulin resistance, potentially by causing conformational changes and reducing the availability of insulin receptors. Furthermore, L-asparaginase may have a direct toxic effect resulting in pancreatitis, which can contribute to TIH. The combination of corticosteroids and L-asparaginase synergistically heightens glucose intolerance and TIH [4]. However, there is a gap in the literature regarding prospective toxicity studies.

Complications of TIH during ALL therapy include diabetic ketoacidosis, an increased risk of infections such as cellulitis and fungemia, and a higher incidence of febrile neutropenia. Febrile neutropenia was observed in 23 of our patients, of which 13 patients had culture-positive sepsis, primarily caused by Gram-negative organisms. Notably, one patient developed cerebral aspergillosis, whereas 3 others had pulmonary aspergillosis, all during the induction phase. Furthermore, four patients with febrile neutropenia presented with neutropenic enterocolitis, and one showed symptoms of lower limb cellulitis. To summarize, in patients with TIH, the incidence of febrile neutropenia and culture positive sepsis was high, that is, 42.6% and 24.1%, respectively, as compared to patients who did not develop hyperglycemia where the incidence of the mentioned events was 27.9% and 16.6%, respectively. These findings highlight the increased risk of neutropenia and infections along with hospitalizations due to hyperglycemia, the need for vigilant monitoring and timely inter-

Change in Glucose (mg/dL)	Mean ± SD	Median (IQR)	Min - Max
Day 1	-6.77 ± 36.95	-13.00 (-31.00-7.00)	-67.0 - 111.0
Day 2	-17.76 ± 43.17	-26.00 (-44.50-8.50)	-107.0 - 93.0
Day 3	-38.46 ± 42.76	-45.00 (-69.00--15.50)	-129.0 - 69.0
Day 4	-64.04 ± 33.57	-64.00 (-83.50--47.00)	-141.0 - 55.0
Day 5	-83.10 ± 27.03	-83.00 (-104.50--64.00)	-147.0 - 0.0
Day 6	-99.15 ± 21.48	-102.00 (-113.50--83.50)	-146.0 - -31.0
Day 7	-109.25 ± 22.81	-111.00 (-124.00--92.50)	-156.0 - -53.0

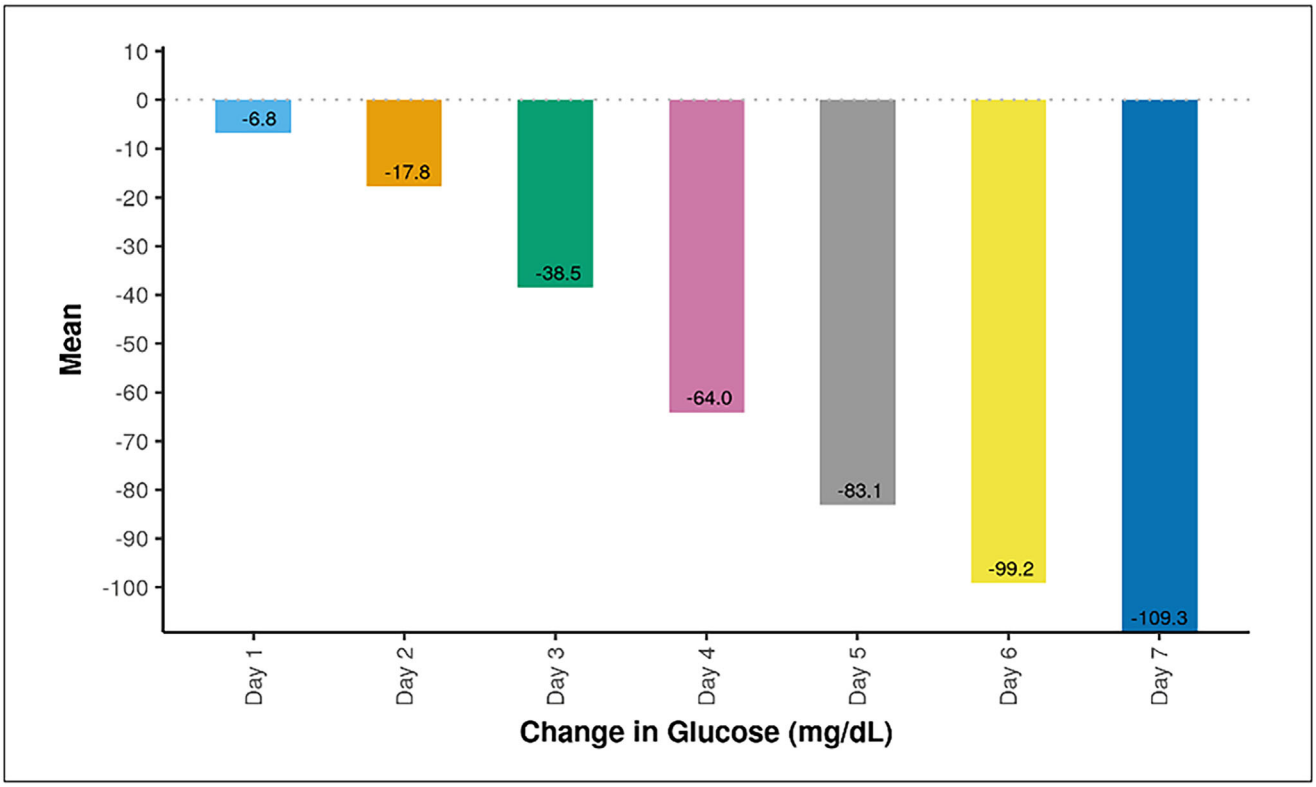

FIGURE 1 | Mean change in glucose level (mg/dL) from Day 1 to 7.

vention in managing infections during ALL treatment, especially in the background of TIH.

The impact of hyperglycemia on overall outcomes in ALL presents a mixed picture. An analysis of four consecutive pediatric ALL clinical protocols from St. Jude Children's Research Hospital (1991 to 2007) found no significant differences in clinical remission rates, event-free or overall survival, cumulative incidence of relapse, or types of infections between patients with and without hyperglycemia [5]. Conversely, a more recent North American study highlighted that patients who developed TIH during induction chemotherapy faced increased risks, including higher rates of intensive care unit admission and mortality. These patients also experienced a greater likelihood of serious infections, extended hospital stays, disease relapse, and a higher need for transplants, ultimately leading to increased healthcare costs [6]. These findings underscore the complexity of the role of hyperglycemia in the management of ALL and the necessity for tailored approaches to mitigate its potential adverse impact.

The most consistently identified risk factor for hyperglycemia in this population is increased age, with a common cutoff being 10 years or older, as highlighted in several studies. Our review aligns with this finding, indicating that older age correlates with a higher risk of TIH, particularly among preadolescent and adolescent patients. Similar findings were reported by Pui et al. and Koltin et al., indicating that children aged 10 years and older are at an increased risk of developing TIH compared to their younger counterparts. This age-related effect likely reflects the heightened insulin resistance associated with gonadal steroids

during puberty [7–9]. Disease- and treatment-related risk factors, such as lineage, treatment protocol, and white blood cell count at diagnosis, have not been associated with hyperglycemia or ketoacidosis [3, 7]. Ochola et al. suggested that high leukocyte count was a predisposing factor for hyperglycemia [10]. In contrast, even after adjusting for age related values, studies by Koltin et al. and Ahammed found no significant association between the initial leukocyte count and the frequency of hyperglycemia, unlike findings reported in a previous study [9, 11]. In our study, 44.4% ($n = 24$) of patients with documented hyperglycemia had a white blood cell count of 20×10^9/L, with nearly half (58.3%, $n = 14$) exhibiting hyperleukocytosis. However, the results did not reach statistical significance ($p = 0.08$), indicating no strong correlation between the presence of hyperleukocytosis and the risk of TIH in our cohort. The influence of age, hyperleukocytosis, and steroid type on the incidence of TIH cannot be conclusively determined from our study due to the small sample size and limited statistical power. It remains uncertain whether these factors may demonstrate a significant effect in a larger, adequately powered cohort. Ahammed, in their study, identified older age, obesity or being overweight, a positive family history of diabetes mellitus, and patients receiving Regimen B according to the UK-ALL 2003 (modified) protocol (having a higher cumulative dose of anthracyclines, cyclophosphamide, and cytarabine) as being associated with an increased risk of hyperglycemia [11]. In our study population, 63% ($n = 34$) had a normal BMI, indicating a generally healthy weight status. This was followed by 22.2% ($n = 12$) overweight, and only 7.4% ($n = 4$) were obese. These findings underscore the importance of addressing weight management and metabolic health in children with ALL.

Insulin has traditionally been used to manage TIH in ALL. However, daily subcutaneous injections can lead to anxiety, pain, and discomfort among children, often resulting in discontinuation and non-compliance, which negatively impacts their quality of life. Additionally, the challenges of closely monitoring food intake and meal timings can increase the incidence of hypoglycemic episodes, further complicating insulin therapy. Oral hypoglycemic agents have not been extensively studied in this context. Metformin, an oral medication with a favorable side effect profile approved for pediatric use in managing dysglycemia and insulin resistance, has been suggested as a safe and reasonably effective option. In our study, the median starting dose of metformin was 250–500 mg/day (range 500–2000 mg). Metformin was typically continued until the completion of corticosteroid therapy. Glycemic control was achieved with metformin alone in 36 patients during induction, whereas 11 required the addition of insulin. Of the patients who developed hyperglycemia during re-induction, seven required dual therapy with both oral metformin and an insulin analogue. In all, 36 out of the 49 patients who developed TIH during induction were successfully managed with metformin alone. Likewise, 15 out of 22 patients with dysglycemia during re-induction were treated with metformin as a single agent. Importantly, all patients successfully discontinued their medications once corticosteroids were tapered, and there were no long-term hyperglycemia-related issues to leukemia treatment.

A retrospective analysis by Bostrom et al. found that 17 children with TIH on ALL therapy required metformin for a median of 6 days (range: 2–46 days), with doses ranging from 100 to 2000 mg/day. Twelve patients did not need insulin for blood sugar control [2]. Seelig et al. conducted a randomized controlled trial involving adult patients receiving steroids for various indications, showing that those treated with metformin maintained normal median glucose levels during an oral glucose tolerance test after 4 weeks of steroid therapy, unlike control patients [12]. Similarly, Wallace and Metzger demonstrated that metformin could be a potential agent for managing steroid-associated dysglycemia in adults with leukemia [13]. Ochola et al. randomized adults over 18 years with hematolymphoid malignancies receiving high-dose steroids into two groups: one receiving standard care and the other receiving standard care plus metformin (850 mg once daily for 2 weeks, followed by 850 mg twice daily for another 2 weeks). The control group saw 72.7% developing prediabetes based on fasting glucose and 54.5% using 2-h postprandial glucose. In contrast, only one participant in the metformin group developed prediabetes based on fasting glucose, and none did using the 2-h postprandial measurement. The effectiveness of metformin as a prophylactic measure was further supported in this prospective randomized study of non-diabetic cancer patients on high-dose prednisone-based chemotherapy [10].

Additionally, metformin has interesting off-target effects that may benefit patients with malignancies, potentially due to its inhibition of AMPK and its downstream targets like mTOR or AKT. Targeting mTOR has shown benefits in childhood ALL [14, 15]. Furthermore, metformin may offer protection against anthracycline cardiotoxicity, as indicated in several studies [11, 14–16]. Concerns about increased toxicity of metformin due to concurrent chemotherapy or comorbid conditions were not observed in our patients. In fact, the risk of hypoglycemia is likely greater with insulin. Roberson et al. described six ALL patients who developed diabetic ketoacidosis treated with insulin, with four experiencing hypoglycemia due to insulin over-treatment [17]. According to Oyer et al., "since there is no evidence proving the benefits of tight control in steroid-induced diabetes, ensuring safety and avoiding hypoglycemia are equally important goals." Thus, metformin is preferable due to its lower risk of hypoglycemia [18].

We initiated metformin therapy for patients with a random BG level exceeding 200 mg/dL or a fasting BG level above 125 mg/dL, provided that they had no significant comorbidities like tumor lysis syndrome, ketonuria, or significant dehydration. For patients with BG levels over 300 mg/dL or those with other comorbidities, or if optimal control was not achieved with 1500 mg of metformin, we considered a short course of insulin analogues as a complementary therapy. These criteria were defined in accordance with recent guidelines for diabetes management in children and adolescents [3]. Elevated hepatic enzymes, often seen in ALL patients, were not considered a contraindication for metformin use. The leukemia control in our patients with hyperglycemia as evaluated by the MRD was non-inferior to the population without TIH with only one patient with refractory disease who then underwent a stem cell transplant and is on follow-up.

Limitations of metformin administration for managing hyperglycemia in ALL include the lack of strong evidence regarding its efficacy, difficulties in rapidly titrating doses based on blood sugar levels, and concerns about its side effect profile and drug

interactions in critically ill children. Further, larger prospective studies are needed to address these issues.

5 | Conclusions

In our experience, metformin shows promise as a potential therapeutic option for managing TIH in children with ALL and could be used as a monotherapy for 73.4% of our patients during induction and 68.1% in re-induction. It may obviate or reduce the need for insulin with its attendant difficulties of hypoglycemia, subcutaneous administration, and frequent blood sugar monitoring. Its favorable safety profile, ability to improve insulin sensitivity, and potential benefits in metabolic health make it a valuable option in this setting. In addition, metformin in combination with chemotherapy may theoretically improve cure by potentially inhibiting mTOR, an active target in leukemia cells. As cardiotoxicity is a significant concern in ALL survivors, the additional benefit of a possible reduction in this risk would also be a welcome benefit of metformin [19]. However, further research is essential to establish optimal dosing, long-term effects, and specific outcomes in this vulnerable population. Collaborative efforts among clinicians, researchers, and families will be crucial in maximizing the benefits of metformin while ensuring safe and effective care for these young patients.

Acknowledgments

The authors have nothing to report.

Ethics Statement

This study was conducted in accordance with the ethical standards of the institutional and national research committee and the Declaration of Helsinki. Ethical approval was obtainedfrom the institutional Ethics Committee prior to study initiation. Written Informed consent was obtained from all participants or their parents/local guardians, and assent was obtained from children where appropriate. Participant confidentiality and data privacy was strictly maintained throughout the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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