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ORIGINAL RESEARCH

Hypertriglyceridemia During Anticancer Therapy in Pediatric Patients with Acute Lymphoblastic Leukemia – A Nationwide Experience

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Purpose: In this study, we aimed to assess the demographics and incidence of hypertriglyceridemia (HTG) during acute lymphoblastic leukemia (ALL) treatment, complications related to HTG, and the treatment strategies applied in pediatric patients treated in pediatric hemato-oncology centers in Poland.

Patients and Methods: A total of 72 out of 641 children, aged <18 years with ALL were diagnosed with HTG as a treatment-related complication. Statistical analyses were conducted with a significance level of $\alpha = 0.05$.

Results: The emergence of HTG is a significant complication, with median peak triglyceride levels during treatment reaching 1385.00 mg/dL. Only 5.56% (n = 4) experienced complications. No patients developed pancreatitis. Treatment interruptions were minimal (a median 5.67 days). No children died due to HTG. Management strategies for HTG management included plasmapheresis in 8.3% (n = 6/72). Other therapies – insulin (23.6%, n = 17), heparin (34.7%, n = 25), fibrates (41.7%, n = 30), and omega-3 fatty acids (58.3%, n = 45). A correlation was observed between low antithrombin levels and high TG levels.

Conclusion: This is the first nationwide, multicenter analysis conducted across pediatric hemato-oncology centers in Poland evaluating HTG during ALL therapy. HTG occurred in 11.1% of children in the analyzed cohort, and 72% of these cases were grade 3 or 4. With the management strategies applied, severe complications were uncommon and chemotherapy interruptions were generally short. Our findings support the effective triglyceride monitoring; however, triglyceride measurements are currently not standardized and are not performed at predefined time points during treatment. The observed association between low antithrombin levels and high triglyceride concentrations may help identify patients who require closer surveillance. Further prospective studies are needed to define risk factors, optimize prevention and treatment strategies and explore long-term outcomes.

Keywords: lipid disorders, childhood leukemia, supportive care, toxicities

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Introduction

Acute toxicities remain significant complications during therapy for childhood acute lymphoblastic leukemia (ALL), despite advances in supportive care. Hypertriglyceridemia (HTG) is frequently reported as a non-infectious acute adverse effect in children and adolescents undergoing anti-leukemic treatment.[1] HTG is primarily associated with the administration of glucocorticoids and asparaginase, both of which are essential components of effective leukemia therapy.[1,2] Reported incidence rates of HTG in previous studies range from 6.7% to 85% (median 27%).[3] The underlying mechanisms are not fully understood.[2,3] HTG is thought to result from increased hepatic production of very low-density lipoproteins combined with reduced activity of lipoprotein lipase, an enzyme responsible for clearing triglyceride-rich lipoproteins from the bloodstream. HTG has been linked to an elevated risk of acute pancreatitis, osteonecrosis (ON), and thrombosis.[1,3–6,] Preventive strategies include dietary modifications, fibrates, insulin infusions, heparin infusions, and, in severe cases, plasmapheresis.[2,3] However, evidence remains limited as to whether these interventions translate into a measurable reduction in clinically relevant HTG-related toxicities. Moreover, there are no widely adopted international recommendations regarding routine lipid screening and the optimal schedule for triglyceride monitoring during ALL therapy, which may contribute to under-recognition of asymptomatic or transient HTG and, consequently, underestimation of its true incidence. In addition, standardized international guidance on thresholds for intervention and on the management of hyperlipidemia during ALL treatment is lacking, resulting in substantial variability in real-world monitoring and treatment practices across centers. In this study, we aimed to evaluate the demographics and incidence of HTG during ALL treatment, associated complications, and management strategies applied in pediatric patients treated at hemato-oncology centers across Poland.

Materials and Methods

Study Group

The study protocol was approved by the Ethics Committee of Medical University of Lublin (KE-0254/207/2020). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent for participation and for the publication of anonymized clinical data was obtained from the legal guardians of all pediatric patients included in this study.

A total of 641 patients with newly diagnosed ALL in Polish pediatric hematology centers from 2021–2024 were included in the study. Preliminary findings regarding HTG in pediatric patients with ALL and lymphoma have been reported previously; however, that investigation was limited by a small sample size and was conducted at a single center.[7] To address these limitations, a nationwide study involving all pediatric hemato-oncology centers in Poland was initiated to comprehensively evaluate the prevalence and clinical implications of HTG in this patient population.

Patients were treated according to the AIEOP-BFM ALL 2017 Poland (International Collaborative Treatment Protocol for Children and Adolescents with Acute Lymphoblastic Leukemia) protocol. Glucocorticoids (prednisone, dexamethasone|) and asparaginase are administered together during the induction (protocol I), consolidation B extended, high risk blocks, reinduction (protocol II) and protocol III phases of the protocol.

Given the retrospective, nationwide multicenter nature of the study, laboratory monitoring followed local scheme at each participating center and was not fully standardized. Triglyceride levels were assessed as part of routine laboratory testing during treatment with steroids and peg-asparaginase and/or when clinically indicated. Pancreatic enzymes (amylase and/or lipase) were measured after administration of peg-asparaginase and when clinically indicated, particularly in the presence of abdominal symptoms or severe hypertriglyceridemia.

Classification of the severity of HTG. HTG has been defined and graded according to the US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. Grades of severity according to the CTCAE v5.0 scale (Table 1).[8]

Table 1 CTCAE V.5.0 Scale for HTG

Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Triglyceride concentration	150 mg/dl–300 mg/dl; 1.71 mmol/L–3.42 mmol/L	>300 mg/dl–500 mg/dl; >3.42 mmol/L–5.7 mmol/L	>500 mg/dl–1000 mg/dl; >5.7 mmol/L–11.4 mmol/L	>1000 mg/dl; >11.4 mmol/L; life-threatening complications	death

Statistical Analysis

Statistical analyses were conducted with a significance level of $\alpha = 0.05$. The normality of data distributions for continuous variables was assessed using the Shapiro–Wilk test. Continuous variables not conforming to a normal distribution were reported as medians, with interquartile ranges (IQRs) defined by the first and third quartiles. Categorical variables were summarized using absolute frequencies (n) and percentages (%). Differences in numerical variables between two independent groups were evaluated using the Wilcoxon rank-sum test for non-parametrically distributed data. Independence between categorical variables was assessed using Pearson's chi-square test; Fisher's exact test was employed when expected frequencies were low to ensure robust inference. Spearman rank-order correlation coefficients (ρ, rho) were calculated to assess associations between changes in laboratory parameters from ALL diagnosis to nadir or peak values during treatment in pediatric ALL patients. All available pairwise observations to maximize data retention while accounting for varying sample sizes across parameters (n = 32–72), thereby excluding cases with missing values for each specific pair of variables. P-values were adjusted using Holm's method to control the family-wise error rate in multiple comparisons. For the analysis of changes in triglycerides (TG) from baseline to post-treatment, robust linear regression (RLM) was performed to estimate the effects of baseline, treatment, and complication parameters, adjusted for age and gender. The RLM model, robust to outliers and non-normal residuals, calculated beta coefficients (β) representing the change in TG (mg/dL) per unit increase in continuous predictors or for specified category comparisons, with 95% confidence intervals (CIs) and p-values which were estimated by asymptotic approximation of the *t* test statistic.

Results

Patient Characteristics

A total of 72 out of 641 children, aged 0.08–17.87 years with ALL described the clinical profile and management of HTG as a treatment-related complication (Table 2). There are no significant differences between these groups.

Details of the HTG cohort were presented in Table 3.

Patient Demographics and Clinical Profile

The demographic and medical history profile reveals a median age of 9.36 years (IQR: 3.86, 12.99), with a slight predominance of females (55.6%, n = 40) over males (44.4%, n = 32), though this sex difference is not statistically significant (χ^2-test, $p > 0.05$). Family history of lipid disorders is rare (1.35%, n = 1), implying that HTG in this cohort is

Table 2 Comparison the Group Patients with and without HTG

Characteristic	Whole Cohort (n = 641)	Patients with HTG (n = 72)	Patients Without HTG (n = 569)	p-value (Pearson χ^2)
Number of Patients	641 (100%)	72 (11.2%)	569 (88.8%)	–
Sex				
Female	299 (100%)	40 (13.4%)	259 (86.6%)	0.174
Male	337 (100%)	32 (9.4%)	305 (90.5%)	0.174
Immunophenotype				
B	560 (100%)	62 (11.1%)	498 (88.9%)	0.809
T	81 (100%)	9 (11.1%)	72 (88.9%)	0.896

Table 3 Baseline Characteristics, Laboratory Findings in Patients with ALL and Laboratory Findings, Treatment Responses, and Outcomes in Patients with ALL: A Cohort Analysis

Characteristic	N	Distribution
A		
1. Demographics and medical history		
Age (years), *Mdn* (*IQR*)	72	9.36 (3.86,12.99)
Sex, n (%):	72	
Female		40 (55.5%)
Male		32 (44.4%)
Family history of lipid disorders, n (%)	72	1 (1.4%)
2. Disease classification and grading, n (%)		
CTCAE v.5.0 grade	72	
1		9 (12.5%)
2		11 (15.2%)
3		11 (15.2%)
4		41 (56.9%)
Immunophenotype	72	
B-ALL		62 (86.1%)
MPAL		1 (1.4%)
T-ALL		9 (12.5%)
Risk group:	72	
Early HR		3 (4.2%)
Early non HR		5 (6.9%)
HR		25 (34.7%)
MR		15 (20.8%)
SR		24 (33.3%)
3. Laboratory results at ALL diagnosis, Mdn (IQR)		
WBC Count (x10^3/μL)	72	11.86 (3.22, 43.25)
Triglyceride level (mg/dL)	38	163.50 (114.00, 220.00)
ALT level (U/L)	72	15.50 (10.00, 22.00)
AST level (U/L)	71	32.00 (22.50, 39.00)
Bilirubin level (mg/dL)	72	0.36 (0.23, 0.53)
Total protein level (g/L)	58	6.29 (6.00, 6.74)
Sodium level (mmol/L)	72	139.00 (138.00, 140.00)
Antithrombin III level (%)	57	1.06 (0.91, 1.18)
D-Dimer level (ng/mL)	50	1,305.00 (806.00, 2,054.00)
Fibrinogen level (g/L)	70	3.52 (2.58, 4.41)
Amylase level (U/L)	41	38.00 (26.00, 48.00)
Lipase level (U/L)	40	12.00 (9.00, 25.75)
CRP level (mg/dL)	72	8.53 (1.78, 23.42)
3B		
1. Peak and nadir laboratory values during treatment, Mdn (IQR)		
Peak triglyceride level (mg/dL)	72	1.385.00 (525.00, 2,533.00)
Peak amylase level (U/L)	64	49.00 (35.00, 60.00)
Peak lipase level (U/L)	65	32.00 (22.00, 61.00)
Peak CRP level (mg/dL)	72	3.00 (0.69, 10.47)
Peak ALT level (U/L)	72	169.00 (107.00, 300.00)
Peak AST level (U/L)	70	88.50 (52.50, 176.00)

(*Continued*)

Table 3 (Continued).

Characteristic	N	Distribution
Peak bilirubin level (mg/dL)	72	1.29 (0.74, 1.89)
Nadir sodium level (mmol/L)	72	132.00 (130.00, 134.50)
Nadir total protein level (g/dL)	61	4.70 (4.14, 5.00)
Nadir antithrombin III level (%)	66	0.51 (0.40, 0.60)
Nadir fibrinogen level (g/L)	67	1.26 (0.76, 3.50)
Peak D-Dimer level (ng/mL)	39	700.00 (408.70, 1,180.00)
Nadir WBC count ($\times 10^3/\mu L$)	72	1.05 (0.50, 1.87)
Nadir neutrophil count ($\times 10^3/\mu L$)	72	0.23 (0.07, 0.74)
2. Phase therapy for HTG		
Protocol I	72	23 (32%)
Cosolitadion A	72	10 (1.4%)
Consolidation B extended	72	8 (11.1%)
Consodation B short	72	2 (2.8%)
Protocol II	72	18 (25%)
High risk blocks	72	6 (8.3%)
Protocol III	72	5 (7%)
3. Interventions for HTG, n (%)		
Plasmapheresis performed	72	6 (8.3%)
Insulin therapy	72	17 (23.6%)
Heparin therapy	72	25 (34.7%)
Fibrate therapy	72	30 (41.7%)
Omega-3 fatty acid supplementation	72	42 (58.3%)
4. Outcome, adverse events or interruptions, Mdn (IQR)		
Complications, n (%)	72	4 (5.6%)
Triglyceride level post-treatment (mg/dL)	72	136.00 (106.00, 206.75)
Duration of Treatment Interruption (days)	72	5.67 (0.0, 9.0)
Medications from the protocol due to hypertriglyceridemia, n (%)	72	1 (1.4%)
Death due to hypertriglyceridemia and related complications, n (%)	72	0 (0%)

predominantly iatrogenic, driven by ALL therapy rather than genetic predisposition. Disease characteristics further define this profile, with the majority (86.1%, n = 62) exhibiting B-cell ALL, most patients had Grade 4 HTG (56.9%, n = 41) and were stratified to HRG (34.7%, n = 25). Baseline laboratory results at ALL diagnosis, including a median triglyceride level of 163.50 mg/dL (IQR: 114.00, 220.00, n = 38), indicate low elevation (Grade 1). The median duration from ALL diagnosis to the onset of HTG was 1.95 months (IQR: 1.25–6.54 months), indicating an early onset following diagnosis of this metabolic complication, potentially attributable to induction chemotherapy regimens or disease-related factors. The emergence of HTG is a significant complication, with median peak triglyceride levels during treatment reaching 1385.00 mg/dL (IQR: 525.00, 2, 533.00, n = 72), indicating severe HTG (>1000 mg/dL) in a substantial proportion of patients.

Therapeutic Interventions and Responses

Management strategies for HTG included plasmapheresis in 8.3% (n = 6/72), consistent with practices for severe HTG (>1000 mg/dL) to prevent complications. Other therapies – insulin (23.6%, n = 17), heparin (34.7%, n = 25), fibrates (41.7%, n = 30), and omega-3 fatty acids (58.3%, n = 45) – reflect a multi-modal approach.

Clinical Outcomes and Complications

Only 5.56% (n = 4/72) experienced complications, such as diabetes (1 pts), osteonecrosis (2 pts), Hepatitis (1 pt). Pancreatitis was not observed in any patient. Post-treatment triglyceride levels normalized to a median of 136.00 mg/dL (IQR: 106.00, 206.75, n = 70), demonstrating effective metabolic control. Treatment interruptions were minimal and transient, with a median duration of 5.67 days (IQR: 0.00, 9.00, n = 72, range: 0–41 days). In one patient, chemotherapy has been reduced; instead of two high-risk courses and protocol III, blinatumomab was used (4 courses). There were no HTG-related fatalities. Details were presented in Table 4.

ALL Diagnosis to Peak/Nadir Values During Treatment in Pediatric ALL Patients

This study evaluates potential associations between changes in 13 laboratory parameters, specifically as white blood cell count (WBC, $\times 10^3/\mu L$), triglycerides (TG, mg/dL), alanine aminotransferase (ALT, U/L), aspartate aminotransferase (AST, U/L), bilirubin (mg/dL), total protein (g/L), sodium (mmol/L), antithrombin III (%), D-dimer (ng/mL), fibrinogen (g/L), amylase (U/L), lipase (U/L), and C-reactive protein (CRP, mg/dL) (Table 5).

The analysis of Spearman rank-order correlations between changes in laboratory parameters from ALL diagnosis to nadir or peak values during treatment visualized in Figure 1.

Changes in triglycerides (TG; mg/dL; peak) from baseline showed a moderate positive Spearman correlation with changes in white blood cell count (WBC; $\times 10^3/\mu L$; nadir; Spearman's $\rho = 0.46$), suggesting that greater increases in TG during treatment were associated with a smaller magnitude of WBC suppression. This highlights a potential link between HTG, induced by asparaginase and steroid therapy, and increased myelosuppression, which may elevate infection risk due to neutropenia, necessitating monitoring of lipid and hematological changes to guide supportive care like G-CSF or antibiotics. A moderate negative correlation with changes in lipase level (U/L, peak, rho = −0.51) indicates that larger TG increases are associated with smaller or negative changes in lipase, arguing a possible pancreatic response to HTG, warranting monitoring of TG and lipase changes to assess pancreatitis risk and consider interventions like plasmapheresis or dietary adjustments. Changes in TG also demonstrated weaker correlations, including a positive association with changes in amylase (U/L, peak, rho = 0.33), supporting a link with pancreatic enzyme changes, and negative associations with changes in sodium (mmol/L, nadir, rho = −0.30) and antithrombin III (%, nadir, rho = −0.51), indicating associations with electrolyte imbalances and coagulopathy, respectively, requiring monitoring and management of these parameters.

Moderate positive correlations between changes in C-reactive protein (CRP, mg/dL, peak) and changes in fibrinogen (g/L, nadir, rho = 0.32) and D-dimer (ng/mL, peak, rho = 0.22) imply associations between increased inflammation and altered coagulation, indicating a need for monitoring these changes to manage thrombosis risk. A moderate negative correlation between changes in lipase (U/L, peak) and amylase (U/L, peak, rho = −0.42) indicates variable pancreatic enzyme responses, requiring monitoring to evaluate pancreatitis risk.

Associations Between Baseline Laboratory Parameter Values and Changes During Treatment in Pediatric ALL Patients

This study examined whether higher baseline values of laboratory parameters at ALL diagnosis are associated with greater or lesser changes in those parameters from diagnosis to nadir or peak values during treatment, potentially identifying predictive patterns for treatment-related complications such as HTG, hepatotoxicity or myelosuppression.

Spearman rank-order correlations (Table 6) revealed significant associations: higher baseline white blood cell count (WBC, $\times 10^3/\mu L$) was strongly negatively correlated with changes in WBC (rho = −0.98, 95% CI: −0.99, −0.97, $p < 0.001$), indicating greater decreases in patients with higher baseline values, supporting increased myelosuppression risk.

Higher baseline aspartate aminotransferase (AST, U/L) demonstrated a moderate negative correlation with changes in AST (rho = −0.42, 95% CI: −0.60, −0.19, $p < 0.001$), demonstrating less increases in patients with higher baseline levels, consistent with hepatotoxicity.

Table 4 Characteristic Features of Children, Who Underwent Plasmapheresis

N	Sex	Age	ALL Type	GR	Grade	Phase Therapy	Peak TG [mg/dl]	Peak Amylase [U/l]	Peak Lipase [U/l]	Peak CRP [mg%]	Peak ALT [U/l]	Peak AST [U/l]	Previous Therapy	Complication of HTG
1	M	13,0	B-ALL	MR	4	IA	1135	40	47	1,36	603	550	Insulin therapy/heparin/ fibrate/omega-3 fatty acid	Osteonecrosis, hepatitis
2	M	13,0	B-ALL	MR	4	IIA	1779	47	34	13,57	1052	530	Insulin therapy/heparin/ fibrate/omega-3 fatty acid	Osteonecrosis, hepatitis
3	F	4,6	B-ALL	SR	4	IIA	1550	33	73	18,27	32	37	Insulin therapy/omega-3 fatty acid	–
4[a]	M	14,3	B-ALL	HR	4	Cons. Ext + BZM	2534	47	64	41,56	160	95	Insulin therapy	–
5	F	15,7	B-ALL	SR	4	Cons. A	1078	28	22	2,51	357	296	Insulin therapy/fibrate/ omega-3 fatty acid	Hepatitis
6	F	12,1	B-ALL	HR	3	IIIA	4018	32	93	8,7	592	261	Insulin therapy/omega-3 fatty acid	Hepatitis

Notes: [a]this patient received 4 course of blinatumomab, instead of two high risk course and protocols III; Cons. Extended + BZM = Consolidation Extended plus Bortezomib.

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Table 5 Changes in Laboratory Parameters from ALL Diagnosis to Nadir/Peak Values During Treatment in Pediatric ALL Patients

Characteristic	N	Change from ALL Diagnosis to Nadir/Peak[a]
WBC (×10³/μL), Nadir	72	−10.07 (−44.15, −2.25)
Total Protein (g/L), Nadir	51	−1.52 (−2.30, −1.10)
Sodium (mmol/L), Nadir	72	−6.00 (−9.00, −5.00)
Antithrombin III (%), Nadir	53	−0.51 (−0.66, −0.37)
Fibrinogen (g/L), Nadir	61	−1.92 (−2.79, 0.51)
Triglycerides (TG, mg/dL), Peak	37	1,160.00 (426.00, 2,461.00)
Alanine Aminotransferase (ALT, U/L), Peak	72	150.00 (67.00, 289.00)
Aspartate Aminotransferase (AST, U/L), Peak	67	42.00 (14.00, 289.00)
Bilirubin (mg/dL), Peak	72	0.82 (0.32, 1.61)
D-Dimer (ng/mL), Peak	32	−320.00 (−1,181.50, 290.75)
Amylase (U/L), Peak	40	10.50 (1.00, 23.00)
Lipase Level (U/L), Peak	40	16.50 (4.75, 31.50)
C-Reactive Protein (CRP, mg/dL), Peak	72	−2.46 (−12.88, 1.86)

Notes: [a]Median (interquartile range, IQR) for changes calculated as nadir/peak value minus baseline value at ALL diagnosis. Note: N varies due to missing data for some parameters.

Antithrombin III (%, nadir), fibrinogen (g/L, nadir), and sodium (mmol/L, nadir) were strongly negatively correlated with their changes (rho = −0.66, −0.62, −0.44, respectively; all $p < 0.001$), indicating larger decreases in patients with higher baseline values, reflecting inflammation, coagulopathy, and electrolyte imbalances.

However, higher baseline triglycerides (TG, mg/dL) demonstrated a weak negative correlation with changes in TG (rho = −0.23, 95% CI: −0.52, 0.11, p = 0.166), and higher baseline alanine aminotransferase (ALT, U/L) demonstrated

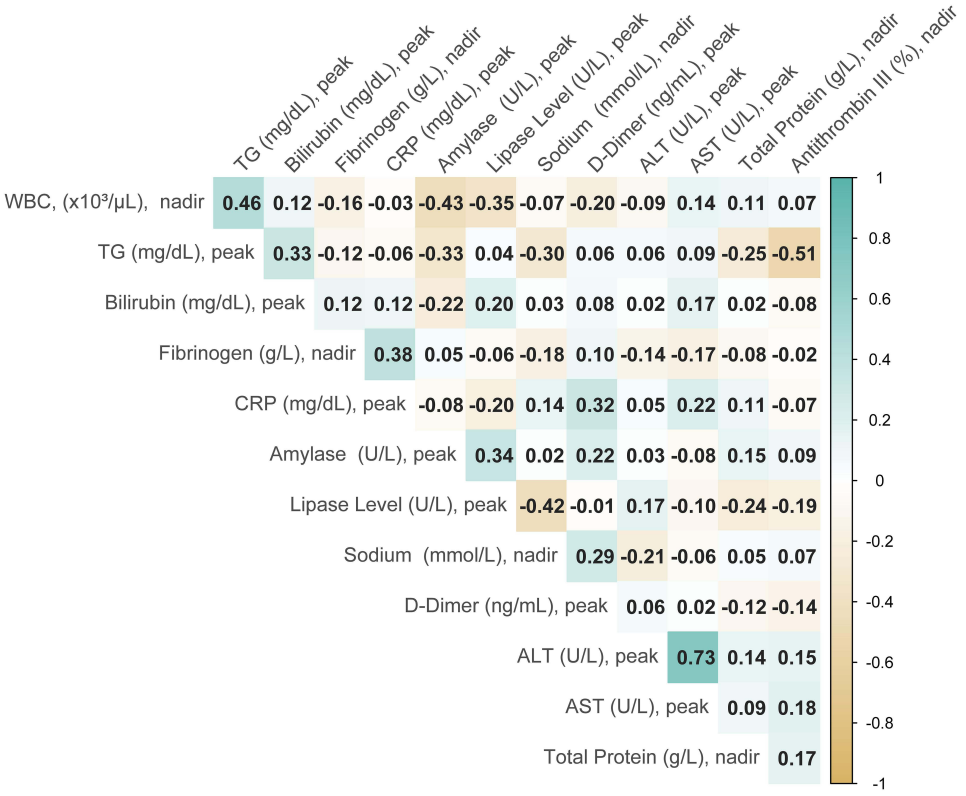

Figure 1 Spearman correlation matrix of parameter changes in pediatric ALL.

Table 6 Associations Between Baseline Laboratory Parameter Values and Changes During Treatment in Pediatric ALL Patients

Parameter	n	Spearman Rho[a]	95% CI	p-value[b]
Triglycerides (TG, mg/dL)	37	−0.23	−0.52, 0.11	0.166
White Blood Cell Count (WBC, ×10^3/μL)	71	−0.98	−0.99, −0.97	< 0.001
Alanine Aminotransferase (ALT, U/L)	72	−0.16	−0.39, 0.08	0.167
Aspartate Aminotransferase (AST, U/L)	67	−0.42	−0.60, - 0.19	< 0.001
C-Reactive Protein (CRP, mg/dL)	72	−0.70	−0.80, −0.56	< 0.001
Antithrombin III (%, nadir)	53	−0.66	−0.79,-0.47	< 0.001
Fibrinogen (g/L, nadir)	61	−0.62	−0.75, −0.43	< 0.001
Sodium (mmol/L, nadir)	72	−0.44	−0.61, −0.22	< 0.001

Notes: [a]Spearman rho correlation coefficient between baseline value and change (nadir/peak – baseline); positive rho indicates higher baseline values are associated with larger increases (or smaller decreases), negative rho indicates higher baseline values are associated with larger decreases (or smaller increases); [b]P-value adjusted for multiple comparisons using Holm's method.

a weak negative correlation with changes in ALT (rho = −0.16, 95% CI: −0.39, 0.08, p = 0.167), revealing limited predictive power for HTG or hepatotoxicity.

Finally, higher baseline C-reactive protein (CRP, mg/dL) demonstrated a strong negative correlation with changes in CRP (peak – baseline, rho = −0.70, 95% CI: −0.80, −0.56, p < 0.001), indicating larger decreases (or smaller increases) in CRP during treatment in patients with higher baseline values, reflecting a potential resolution or suppression of inflammation due to treatment.

These findings partially support the claim, with strong evidence for myelosuppression, hepatotoxicity, inflammation, and coagulopathy, but not for HTG.

Evaluation of the Influence of Baseline, Treatment, and Complication Parameters on Changes in Triglycerides from Baseline to Post-Treatment in Pediatric ALL Patients

In a cohort of 37 ALL pediatric patients with available data, the median change in TG calculated as post-treatment value minus baseline value was −4.00 mg/dL (IQR: −119.00, 61.00), showing a slight reduction or minimal alteration, with substantial interpatient variability. The robust regression analysis, adjusted for age and gender, of 27–37 pediatric ALL patients treated in Polish pediatric hematology and oncology centers reveals key determinants of changes in TG level from baseline to post-treatment (see Table 7).

Table 7 Effects of Baseline, Treatment, and Complication Parameters on Changes in Triglycerides from Baseline to Post-Treatment in Pediatric All Patients: Robust Regression Analysis is Adjusted for Age and Sex

Predictor	n	β (mg/dL)[a]	95% CI (Lower, Upper)[b]	p-value[c]
CTCAE Grade (1–3 vs 4)	34	−77.81	−221.43, 65.82	0.277
Immunophenotype (B-cell vs T-cell)	37	−85.85	−377.94, 206.24	0.554
Risk Group (Standard vs Others)[4]	37	−93.53	−197.34, 10.28	0.076
WBC Count at ALL Diagnosis (×10^3/μL)	37	−0.52	−1.56, 0.53	0.321
Triglyceride Level at ALL Diagnosis (mg/dL)	37	−1.41	−1.85, −0.97	**< 0.001**
Alanine Aminotransferase (ALT, U/L) at Diagnosis	37	0.06	−1.69, 1.81	0.949
Aspartate Aminotransferase (AST, U/L) at Diagnosis	34	−1.22	−3.31, 0.86	0.239
Bilirubin Level at ALL Diagnosis (mg/dL)	37	44.65	5.70, 83.60	**0.026**
Total Protein Level at ALL Diagnosis (g/L)	28	8.86	−49.65, 67.38	0.757
Sodium Level at ALL Diagnosis (mmol/L)	37	24.62	0.15, 49.09	**0.049**
Antithrombin III Level at ALL Diagnosis (%)	37	280.03	−32.44, 592.49	0.077
D-Dimer Level at ALL Diagnosis (ng/mL)	30	0.00	−0.01, 0.00	0.409

(*Continued*)

Table 7 (Continued).

Predictor	n	β (mg/dL)[a]	95% CI (Lower, Upper)[b]	p-value[c]
Fibrinogen Level at ALL Diagnosis (g/L)	37	0.00	−0.01, 0.00	0.518
Amylase Level at ALL Diagnosis (U/L)	27	1.47	−1.15, 4.09	0.257
Lipase Level at ALL Diagnosis (U/L)	28	−0.65	−2.68, 1.39	0.518
CRP Level at ALL Diagnosis (mg/dL)	37	1.44	−2.07, 4.94	0.410
Steroid Response (Yes vs No)	35	−34.73	−394.75, 325.28	0.845
Plasmapheresis Performed (Yes vs No)	37	358.76	241.75, 475.78	**< 0.001**
Insulin Therapy (Yes vs No)	37	145.16	33.93, 256.40	**0.012**
Heparin Therapy (Yes vs No)	37	−15.73	−127.61, 96.15	0.777
Fibrate Therapy (Yes vs No)	37	−65.25	−174.66, 44.15	0.234
Omega-3 Fatty Acid Supplementation (Yes vs No)	37	102.81	2.61, 203.01	**0.045**
Complications (Yes vs No)	37	226.42	51.54, 401.29	**0.013**
Duration of Treatment Interruption (days)	37	6.08	−0.29, 12.45	0.061

Notes: [a]Beta coefficient (β) represents the change in TG (mg/dL) per unit increase in the predictor or for the specified category comparison, adjusted for age and gender using robust regression; [b]95% confidence interval (lower limit, upper limit) for the beta coefficient; [c]P-value adjusted for age and sex confounders; values <0.05 indicate statistical significance after adjustment; [d]Risk group categories were collapsed into "Small Risk" versus all others (eg, High Risk, Medium Risk) due to sample size constraints; Sample sizes (n) vary due to missing data for some parameters, reflecting the use of complete cases in the robust regression model. P-values < 0.05 were bolded.

Significant predictors of TG changes ($p < 0.05$) include higher baseline triglyceride levels, which demonstrated a significant negative association ($\beta = -1.41$ mg/dL, 95% CI: −1.85, −0.97, $p < 0.001$), indicating smaller increases or larger decreases in TG during treatment, potentially reflecting effective HTG management or regression to the mean, warranting further investigation into lipid-lowering interventions.

Higher baseline bilirubin levels were significantly positively associated with larger TG increases ($\beta = 44.65$ mg/dL, 95% CI: 5.70, 83.60, $p = 0.026$), pointing to a link between hepatic dysfunction and treatment-induced HTG, necessitating monitoring of liver function and lipid changes to prevent complications like pancreatitis.

Higher baseline sodium levels were significantly positively associated with larger TG increases ($\beta = 24.62$ mg/dL, 95% CI: 0.15, 49.09, $p = 0.049$), possibly indicating an electrolyte imbalance influencing lipid metabolism, requiring careful monitoring of sodium and TG changes.

Patients who underwent plasmapheresis experienced significantly larger TG increases ($\beta = 358.76$ mg/dL, 95% CI: 241.75, 475.78, $p < 0.001$), which may reflect selection bias for severe HTG or a rebound effect post-procedure. Those receiving insulin therapy had significantly larger TG increases ($\beta = 145.16$ mg/dL, 95% CI: 33.93, 256.40, $p = 0.012$). Patients receiving omega-3 fatty acid supplementation demonstrated significantly larger TG increases ($\beta = 102.81$ mg/dL, 95% CI: 2.61, 203.01, $p = 0.045$). The relationship between treatment use and higher TG reflects severity-driven initiation (confounding by indication) rather than a causal effect.

Patients with complications had significantly larger TG increases ($\beta = 226.42$ mg/dL, 95% CI: 51.54, 401.29, $p = 0.013$), reflecting a link between HTG-related complications and persistent lipid dysregulation, underscoring the need for aggressive TG management.

Non-significant predictors ($p > 0.05$) included CTCAE grade, immunophenotype, risk group, WBC count, ALT, AST, total protein, antithrombin III, D-dimer, fibrinogen, amylase, lipase, CRP, steroid response, heparin therapy, fibrate therapy, and duration of treatment interruption, highlighting they do not independently influence TG changes after adjustment for age and gender.

Discussion

Hypertriglyceridemia is a common treatment-related toxicity during therapy childhood ALL.

A single center observations of HTG in children with ALL and lymphoblastic lymphoma have been published elsewhere, but that study included only 75 pediatric patients, which limited its generalizability.[7] This study presents

a retrospective analysis ALL patients with treatment-related HTG who were treated in all Polish hemato-oncology centers. We observed HTG incidence in Polish patients was approximately 11%. In other studies, the on-therapy median incidence was 27% (ranged 6.7–85%).[3] There are reports that HTG, assessed as grade 4 according to the CTCAE, occurred more frequently with E. coli asparaginase (PEG-ASP) than with Erwinia asparaginase. [9] Currently, in Poland, PEG-ASP is used due to its lower risk of allergic reactions compared to the native form of the drug and its more effective early response to treatment. The risk of HTG increases when PEG-ASP is applied together with glucocorticoids. Most HTG complications were observed during the induction (32%) and reinduction phases (25%).[2]

In our cohort, both high-risk (HR) and standard-risk (SR) patients demonstrated a similar association with grade 4 HTG. However, literature reports from two studies indicate that HR patients are more frequently linked to grade 4 HTG compared to SR patients, and one study presented no difference between these groups.[10,11]

The consequences of HTG observed during the treatment of ALL may be serious and include osteonecrosis (ON), pancreatitis or thrombosis.[2,3,12] The incidence of osteonecrosis in the NOPHO 2008 study was 6.3%. We observed ON in two (2.8%) children with HTG grade 4. In these patients, plasmapheresis has been used. Laumann et al presented that HTG increased a risk of ON in a meta-analysis of three studies (n = 1088 pts).[3] Bhojwani et al (n = 257, OR: 5.00, CI: 1.79–13.98) and Schmidt et al (n = 165, OR: 9.27, CI: 1.01–84.9) also demonstrated an increased risk of ON in patients with HTG.[9,11] Literature reports on the increased risk of pancreatitis and thrombosis in patients with HTG are inconclusive.[3,10,13] In our study, we did not detect these complications. There are studies, which presented correlation between low antithrombin levels and high TG levels,[10] and we observed similar association.

The options of management in pediatric patients with HTG include: education parents/children, low-fat diet, omega-3 fatty acids, fibrates, heparinization, insulin infusion or plasmapheresis.[14–18] In our cohort, invasive procedures such as plasmapheresis were performed in 6 patients (2 of whom underwent lipid apheresis). Procedures were effective and well tolerated. Of the 13 studies analysed, two reported plasmapheresis and one reported lipid apheresis with a decrease in triglyceride levels.[17–19] Currently, large randomized controlled trials are needed to publish evidence-based guidelines for patients with HTG. Omega-3 fatty acids are now the subject of clinical studies aimed at utilizing them in therapeutic strategies to reduce treatment toxicity, including HTG. In the currently ongoing clinical trial, researchers hypothesize that daily intake of fish oil will prevent the development of hyperlipidemia during the phases of ALL treatment with dexamethasone and PEG-asparaginase compared to placebo, and that fish oil intake may reduce the incidence of severe adverse events associated with ALL treatment (clinicaltrials. gov).[20]

Currently, in Poland, we rely on the recommendations of the Polish Pediatric Oncology and Hematology Society, which were developed on the basis of our experience and literature reports.[20] In this paper, we suggest using two scales to assess the severity of HTG during anticancer treatment: the Ponte di Legno Working Group (PTWG) scale[21] and the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[8] We also described therapeutic recommendations depending on serum triglyceride concentration.[22] However, larger research related to potential risk factors, optimal time points for monitoring TG levels, consequences of HTG in patients (osteonecrosis, thrombosis), and therapeutic strategies for these patients, especially randomized trials, should be considered.

Conclusion

This is the first nationwide, multicenter analysis conducted across pediatric hemato-oncology centers in Poland evaluating HTG during ALL therapy. HTG occurred in 11.1% of children in the analyzed cohort, and 72% of these cases were grade 3 or 4. With the management strategies applied, severe complications were uncommon and chemotherapy interruptions were generally short. Our findings support the effective triglyceride monitoring; however, triglyceride measurements are currently not standardized and are not performed at predefined time points during treatment. Therefore, recommendations for lipid monitoring are necessary. The observed association between low antithrombin levels and high triglyceride concentrations may help identify patients who require closer surveillance. The retrospective design, incomplete laboratory data, and the relatively small HTG subgroup limit causal inference. Further prospective studies are needed to define risk factors, optimize prevention and treatment strategies, and explore long-term outcomes.

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Disclosure

The authors report no conflicts of interest in this work.

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