Impact of Body Mass Index at Diagnosis on Outcomes of Pediatric Stage III and IV Mature B-Cell Non- Hodgkin Lymphomas at South Egypt Cancer Institute: A Prospective Cohort Study

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Abstract:

Background and aim of the study: Nutritional status impacts treatment outcomes in pediatric cancers. This study evaluated the impact of body mass index (BMI) on clinical outcomes and survival in children with stage III and IV mature B-cell non-Hodgkin lymphomas (B-NHL).

Methods: A prospective cohort study enrolled pediatric patients with advanced CD20-positive mature B-NHL at South Egypt Cancer Institute (SECI), Assiut University from 2020-2025. Patients were risk-stratified by the BFM-95 protocol and categorized by BMI. Treatment response (at the end of treatment), event-free survival (EFS), and overall survival (OS) were assessed.

Results: A total of 65 newly diagnosed pediatric patients with stage III and IV mature B-cell NHL were enrolled in the study. The mean age was 7.35 ± 3.9 years (median 6 years) with a male predominance (75.4%). Patients with stage III disease were (69.2%), and 58.4% were classified in the highest risk group (R4). The average BMI was 16.51 ± 2.9 kg/m², with nearly half (49.2%) being of normal weight while undernutrition was identified in 44.7% of cases. Multivariate analysis revealed that each unit increase in BMI was independently associated with a 21% reduction in the hazard of mortality, while it had insignificant effect on OS in univariate analysis as while as EFS.

Conclusions: These findings suggest that BMI is a significant prognostic factor in stage III and IV pediatric mature B-cell lymphomas and should be considered during risk stratification and supportive care planning. Improved nutritional status appears linked to better treatment tolerance and survival outcomes in this aggressive malignancy.

Keywords: Pediatric non-Hodgkin lymphoma, High-risk B-cell lymphoma, Body mass index (BMI), Chemotherapy outcomes, Nutritional status, Rituximab, BFM-95 protocol

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Introduction:

Non-Hodgkin lymphomas (NHLs) are the third most common pediatric malignancy, with mature B-cell subtypes (Burkitt lymphoma (BL), Burkitt leukemia, and diffuse large B-cell lymphoma (DLBCL)) comprising over 60% of cases [1]. These tumors are aggressive, fast-growing, with male predilection and median age of 8 years with a range of 4–14 years, often presenting with extensive extranodal involvement [2].

Treatment outcomes have significantly improved with refinements in classification, advancements in supportive care, and risk adapted chemotherapy according to protocols like LMB or BFM-95 protocols, achieving >90% 5-year survival in standard-risk

patients [3]. However, children with advanced stage group, typically with stage III/IV disease, elevated LDH, and/or CNS involvement face poorer prognoses and require intensified treatment with CD20 monoclonal antibody (rituximab), which increases toxicity risk [1,3].

Nutritional status, particularly BMI, influences chemotherapy metabolism, immune response, and tolerance, and has been linked to outcomes in pediatric cancers [4]. Obesity may impair drug efficacy due to altered pharmacokinetics, while undernutrition increases toxicity risk from reduced physiological reserves [5]. Despite this, data on BMI's role in pediatric B-NHL, especially high-risk cases, remain limited [4,6]. The prospective study aims to fill this gap by evaluating the impact of BMI on the clinical outcome, treatment response, and survival among children with advanced mature B-cell lymphomas treated by modified -BFM-95-based protocol [7].

Methodology:

A prospective cohort study was conducted at the Pediatric Oncology and hematological malignancies Department, South Egypt Cancer Institute (SECI), Assiut University, between April 1, 2020, and April 1, 2025. It included 65 newly diagnosed pediatric patients (aged 2–18 years) with CD20-positive advanced stage III and IV mature B-cell lymphomas (BL, Burkitt leukemia, or DLBCL) classified using the (BFM)-95 risk stratification system as intermediate (R2, R3) or high-risk (R4) after approval by our institute review boards at SECI. Written informed consent was obtained from all patients` guardians or parents.

Included patients were negative for hepatitis B virus [22] , and with adequate organ/cardiac function.

Diagnostic and Nutritional Evaluation

Demographic data, clinical presentation, and physical findings (e.g., lymphadenopathy, hepatosplenomegaly, CNS signs) were recorded. Body mass index for age (BMI/A), which is measured from 2 to 5 years z-scores using WHO z-scores using Anthro software of World Health Organization (WHO) [9], and from 5 to 18 years z-scores using Reference of Growth Parameters for Egyptian School Children and Adolescents aged from 5 to 19 Years [10]. For BMI- for age, it was categorized into three groups: undernourished – patients with z-score > -1 SD from mean BMI-for-age (-1 to -1.99 mild undernutrition, -2 to -2.99 moderate undernutrition, ≤ -3 severe undernutrition); normal – patients between -1 SD and +1 SD from mean BMI/A; and over-nourished – patients > +1 SD from mean BMI/A [>+1SD overweight, >+2SD obese] [8]. These BMI measurements and nutritional categorizations were then used to analyze correlations with clinical outcomes, and survival.

Diagnostic Workup included laboratory tests as CBC, liver/renal function, electrolytes, uric acid (UA) , and LDH levels. Hepatitis screening was mandatory. Histopathology and immunohistochemistry confirmed B-cell phenotype (CD20+, CD79a+, TdT–, CD3–), and cytogenetics identified MYC translocations. Bone marrow and CSF evaluations assessed for marrow/CNS involvement. All patients underwent chest X-rays and abdominal/neck/axillary ultrasound. CT or PET-CT scans were used for detailed assessment; Magnetic Resonance Imaging (MRI) was performed if CNS disease was suspected.

Risk Stratification and Treatment

Patients were classified according to International BFM Study Group [7] as:

- R2: Stage III, LDH <500 U/L
- R3: Stage III/IV, LDH 500–999 U/L, no CNS involvement
- R4: Stage III/IV, LDH ≥1000 U/L and/or CNS involvement

All patients received BFM-95-based chemotherapy [7] . Initial cyto-reduction COP (cyclophosphamide, vincristine, prednisolone) was given for all treatment groups, followed by 4 courses of (A-B-A-B) for R2 patients, 5 courses (AA-BB-CC-AA-BB) for R3 patients and 6 courses (courses as in R3 group but with additional 6th course of CC) for R4 patients. R4 patients also received rituximab (375 mg/m²) on D-5 of each cycle. Intrathecal therapy (methotrexate, cytarabine, hydrocortisone) was given as modified BFM-95 protocol [7].

Early tumor response was assessed on day 7 post-COP: >20% size reduction was considered a good response. Imaging (PET-CT, CT, ultrasound) and marrow/CSF re-evaluation were used to define response. Complete Response (CR) was defined as Complete disappearance of all measurable or evaluable lesions (except bone), no L3 blasts in the bone marrow or in the CSF, while residual disease was defined when 20-99% reduction in the product of the two largest diameters (perpendicular) of measurable lesions and/or in the case of leukemia; 20-99% reduction in the number of L3 blasts in the bone marrow and/or in the CSF.

Statistical Analysis

All data were entered and analyzed using SPSS version 26. Descriptive statistics, including means, standard deviations, medians, interquartile ranges, and percentages, were computed for all patient variables. The chi-square test was used to assess associations between categorical variables, including BMI categories and treatment response. Kaplan–Meier survival analysis was conducted to estimate overall survival (OS) (calculated for all patients as the time interval from date of diagnosis of the disease to date of last follow up or date of death from any cause) and event-free survival (EFS) (calculated for all studied cases as the time interval from the date of admission up to the date of progression, relapse, death from any cause or last follow up , whatever happened first), with the log-rank test used to compare survival differences among risk groups and nutritional categories. Moreover, multivariate Cox proportional hazards regression models were employed to identify significant

prognostic factors influencing OS and EFS, with results reported as hazard ratios (HR) and 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant.

Results:

Demographic and Clinical Characteristics

A total of 65 pediatric patients diagnosed with advanced stage mature B-cell lymphomas were included in this study. The mean age was 7.35 ± 3.9 years (range: 2–17 years), with a median age of 6 years. Males represented the majority (75.4%). Most patients presented with stage III disease (69.2%), and 58.4% were categorized in risk group (R4). The abdomen was the most common primary site of disease (75.4%). The majority of patients (61.5%) were diagnosed with BL, while DLBCL accounted for 30.8%, and Burkitt's leukemia for 7.7%. Bone marrow involvement was noted in 17.2% of the cases (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Value	(%)
Age (years)		
- Mean ± SD	7.35 ± 3.9	
- Median (Range)	6 (2–17)	
Sex		
- Male	49	(75.4%)
- Female	16	(24.6%)
Stage		
- III	45	(69.2%)
- IV	20	(30.8%)
Risk Group		
- R2	17	(26.2%)
- R3	10	(15.4%)
- R4	38	(58.4%)
Primary Site		
- Abdomen	49	(75.4%)
- Neck	11	(16.9%)
- Bone Marrow	5	(7.7%)
- Others*	6	(9.2%)
Pathological subtype		
Burkitt Lymphoma (BL)	40	(61.5%)
DLBCL	20	(30.8%)
Burkitt's Leukemia	5	(7.7%)
Bone Marrow Involvement		
Present	11	(17.2%)
Absent	54	(82.8%)
CNS involvement	10	(15.4%)

*Others include mediastinum, maxilla, paraspinal, rectum, and thigh.

Nutritional Status Assessment

The mean BMI was 16.51 ± 2.9 kg/m², with a median of 16 (range: 12–27). Nearly half of the cohort (49.2%) had a normal BMI, while undernutrition (mild to severe) collectively was observed in 44.7% of patients. A small proportion (6.2%) were classified as overnourished (Table 2).

Table 2: Nutritional Status Based on BMI Z-score Categorization

BMI Category (Z-score)	n	(%)
Normal Weight	32	(49.2%)
Mild under-nutrition	18	(27.7%)
Moderate under-nutrition	4	(6.2%)
Severe under-nutrition	7	(10.8%)
Overnourished	4	(6.2%)

Treatment Outcomes by BMI Category

Patients with normal or overweight BMI had better outcomes, with higher complete response (CR) rates and lower mortality compared to undernourished patients (Table 3). By merging BMI categories into two broader groups, this increased the clarity of comparisons (i.e. the undernourished group included all degrees of wasting (mild, moderate, severe) and normal/overweight group represented better- nourished children) and it is often more useful to simplify categories to emphasize actionable findings as the significantly higher mortality among the undernourished patients.

Univariate & Multivariate Analysis for OS

When stratified by nutritional subgroups, patients with moderate and severe malnutrition had significantly inferior outcomes. The 5- year OS rate was 57.1% in severely malnourished patients, compared to 87.5% in patients with normal or overweight BMI.

To detect the prognostic impact of BMI on survival outcome, it was studied among other known prognostic factors. Despite there was insignificant impact on OS in univariant analysis (HR=0.794 (0.495–1.124), P = 0.167), higher BMI found to be associated with improved survival.

Multivariate Cox regression analysis identified BMI as a statistically significant predictor of survival. Each unit increase in BMI was associated with a 21% reduction in the risk of death (HR: 0.794 (0.506–0.899), p=0.044). Other significant predictors were age, disease stage, risk group, and LDH level as shown in (Table 5).

At a median follow-up of 40 months, the estimated 5-year OS rate was 84.6%. Patients with normal or overweight BMI had significantly better survival compared to undernourished counterparts.

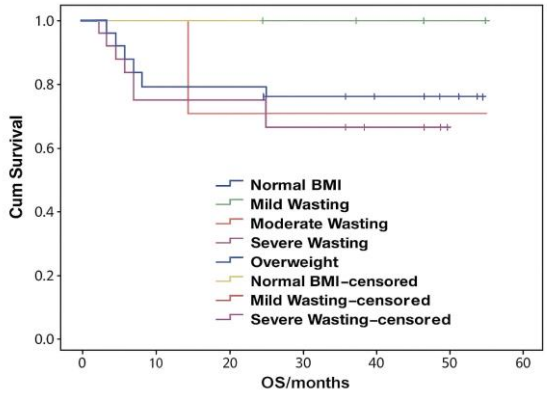

Fig. 1: Kaplan Meier Curve for the 5-year OS according to BMI Category, p-value = (0.044)

Univariate &Multivariate analysis for EFS

On the contrary of OS both univariate and multivariate Cox regression analysis for EFS did not identify BMI as a significant independent predictor (HR: 0.924 (0.730–1.168), p = 0.509). Significant predictors of inferior EFS included being in the R4 risk group (HR: 18.686, p = 0.002), elevated UA levels (HR: 5.953, p = 0.009), and LDH > 1000 U/L (HR: 2.598, p = 0.039). Conversely, having DLBCL pathology was associated with a significantly reduced risk of events (HR: 0.188, p = 0.017) as shown in (Table 6).

Table 3: Treatment Outcomes Stratified by BMI Category

Outcome	Normal/Overnourished (n=36)	Undernourished (n=29)	p-value
Complete Response	31 (86.1%)	19 (65.5%)	0.041*
Residual Disease	2 (5.6%)	3 (10.3%)	0.642
Mortality	3 (8.3%)	7 (24.1%)	0.049*

*Significant at p<0.05

Table 4: The relation between the nutritional status using BMI/A with other clinical criteria of the studied patients

Variable	BMI Categories					P-value*
	Normal (n=32)	Mild under-nutrition (n=18)	Moderate under-nutrition (n=4)	Severe under-nutrition (n=7)	Overnourished (n=4)	
Age:						
- 2-10 (n=50)	27 (84.4%)	12 (66.7%%)	4 (100%)	5 (71.4%)	2 (50%)	= 0.269
->10 (n=15)	5 (15.6%)	6 (33.3%)	0 (0%)	2 (28.6%)	2 (50%)	
Gender:						
- Male (n= 49)	25 (78.1%)	13 (72.2%)	3 (75%)	4 (57.1%)	4 (100%)	= 0.436
- Female (n= 16)	7 (21.9%)	5 (27.8%)	1 (25%)	3 (42.9%)	0 (0%)	
Pathology:						
- BL (n=40)	21 (65.6%)	10 (55.6%)	3 (75%)	4 (57.1%)	2 (50%)	
-DLBCL (n = 20)	10 (31.3%)	8 (44.4%)	0 (0%)	2 (28.6%)	0 (0%)	= 0.210
- Burkitt`s leukemia (n=5)	1 (3.1%)	0 (0%)	1 (25%)	1 (14.3%)	2 (50%)	
Stage:						
- III (n= 45)	22 (68.8%)	15 (83.3%)	1 (25%)	5 (71.4%)	2 (50%)	**= 0.048***
- IV (n= 20)	10 (31.2%)	3 (16.7%)	3 (75%)	2 (28.6%)	2 (50%)	
Risk group:						
- R2 (n= 17)	8 (25%)	8 (44.4%)	0 (0%)	1 (14.3%)	0 (0%)	= 0.351
-R3 (n= 10)	6 (18.8)	0 (0%)	1 (25%)	2 (28.6%)	1 (25%)	
- R4 (n=38)	18(56.3%)	10 (55.6%)	3 (75%5)	4 (57.1%)	3 (75%)	
Initial response:						
> 20% (n= 56)	26 (81.3%)	18 (100%)	3 (75%)	6 (85.7%)	3 (75%)	= 0.664
< 20% (n= 9)	6 (18.8%)	0 (0%)	1 (25%)	1 (14.3%)	1 (25%)	
Fate:						
- Living (n= 55)	26 (81.3%)	15 (83.3%)	3 (75%)	7 (100%)	4 (100%)	= 0.789
- Died (n= 10)	6 (18.8%)	3 (16.7%)	1 (25%)	0(0%)	0 (0%)	

Table 5: Univariat & Multivariate Analysis for overall survival

Variable	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age/years	0.832 (0.449–1.043)	= 0.110	0.824 (0.446–0.992)	**= 0.047**
Sex (Male)	0.292 (0.084–1.011)	= 0.057		
BMI	0.794 (0.495–1.124)	= 0.167	0.794 (0.506–0.899)	**= 0.044**
UA (High)	2.236 (0.607–8.463)	= 0.224		
Stage (IV)	0.465 (0.091–2.283)	= 0.239	0.624 (0.224–0.934)	**= 0.049**
Risk Group (R4)	15.228 (0.898–31.57)	= 0.139	3.597 (1.055–8.839)	**= 0.045**
Pathology (DLBCL)	0.837 (0.170–4.106)	= 0.826		
1ry Site (Abdomen)	3.439 (0.425–17.825)	= 0.247		
LDH (> 1000)	2.138 (0.773–15.284)	= 0.125	3.214 (1.068–6.157)	**= 0.039**
BM Involvement	0.032 (0.001–6.927)	= 0.316		
Response after COP (> 20%)	1.362 (0.170–9.891)	= 0.771		
Receiving RTX	1.359 (0.312–5.942)	= 0.683		

Table 6: Univariate & Multivariate Analysis for Event-Free Survival

Variable	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age/years	0.905 (0.764–1.071)	= 0.246	0.994 (0.750–1.317)	= 0.286
Sex (Male)	0.447 (0.139–1.441)	= 0.178	0.742 (0.145–3.802)	= 0.720
BMI	0.924 (0.730–1.168)	= 0.509		
UA (High)	**4.160 (1.251–9.835)**	**= 0.020**	**5.953 (1.571–22.56)**	**= 0.009**
Stage (IV)	1.237 (0.372–4.108)	= 0.239		
Risk Group (R4)	**8.782 (1.133–28.076)**	**= 0.038**	**18.69 (3.68–31.37)**	**= 0.002**
Pathology (DLBCL)	0.982 (0.525–1.839)	= 0.756	**0.188 (0.047–0.746)**	**= 0.017**
1ry Site (Abdomen)	1.197 (0.270–3.683)	= 0.696		
LDH (> 1000)	**3.098 (1.130–8.491)**	**= 0.028**	**2.598 (1.024–6.801)**	**= 0.039**
BM Involvement	0.944 (0.207–4.311)	= 0.841	**2.157 (1.027–4.904)**	**= 0.038**
Response after COP (> 20%)	1.876 (0.242–14.537)	= 0.547		
Receiving RTX	1.576 (0.497–4.939)	= 0.443		

Discussion:

In this study, we evaluated 65 pediatric patients diagnosed with stage III and IV mature B-cell lymphomas, with a primary focus on demographical, clinical, nutritional, laboratory, and pathological characteristics as well as on treatment response, and survival predictors. The findings of our study are largely consistent with previous reports, while also highlighting some unique patterns observed in our cohort. Our study identified several distinct patterns as, undernutrition was notably prevalent, affecting 44.7% of patients which is higher than typically reported, highlighting the impact of local socioeconomic conditions. second, BMI found as an independent predictor of OS, with better outcomes observed in patients with normal or slightly elevated BMI while interestingly BMI didn`t influence EFS

The mean age of our patients was 7.35 ± 3.9 years, with a median age of 6 years, reflecting a comparably youthful population when juxtaposed with other studies that reported slightly older median ages [10, 11]. A clear male predominance was observed (75.4%), consistent with earlier reports [12–14]. Most patients were identified in stage III (69.2%), while the remaining 30.8% were in stage IV. A large proportion (58.4%) were categorized in the highest risk group (R4), a distribution that differs from larger cohorts where variations in risk-group assignments were noted [14,15]. The abdomen emerged as the most common primary site for the disease (75.4%), which parallels findings in similar studies [12–14].

Nutritional status plays a vital role in treatment outcomes and overall prognosis. Our group had a mean BMI of 16.51 ± 2.9 kg/m², with nearly half of the patients (49.2%) having a BMI within the normal range. However, undernutrition was identified in 44.7% of the children, while a smaller group (6.2%) was overnourished. These data underscore the nutritional challenges encountered in these patients and align with previous evaluations that have found significant associations between nutritional status and prognosis [16,17]. The detailed analysis in table 4 further emphasizes that nutritional status was not an isolated variable but correlated with disease characteristics, undernourished patients were more likely to present with advanced stage (p= 0.048), suggesting that malnutrition reflect the systemic burden of advanced disease.

Pathologically, the spectrum of disease in our study was similar to previous observations. Burkitt lymphoma was documented in 61.5% of cases, followed by DLBCL (30.8%) and Burkitt's leukemia (7.7%). Bone marrow involvement was present in 17.2% of patients, aligning closely with prior studies [12–14,18].

Survival analysis using multivariate Cox regression identified several significant prognostic factors in the studied cohort. Increasing age was associated with a decreased hazard of mortality, with each additional year corresponding to an 18% reduction in risk. More notably, each unit increase in BMI was linked to a 21% decrease in the hazard of death, suggesting an independent protective effect of better nutritional status on OS.

Among clinical variables, stage IV disease surprisingly demonstrated a lower hazard of mortality compared to stage III. This unexpected finding may reflect the impact of intensified therapy typically administered to patients with more advanced disease. Risk stratification remained a powerful predictor of outcome: patients in the R4 group had a 3.6-fold increase in mortality risk compared to those in the R2 group. Similarly, elevated LDH levels (>1000 U/L) were associated with a threefold increase in mortality risk compared to patients with lower LDH levels. At a median follow-up of 40 months, the 5-year OS rate in our cohort was 84.6%, and the EFS rate was 81.5%, consistent with previous literature [17–19,20].

In contrast, the multivariate analysis for EFS did not retain BMI as a statistically significant independent predictor (HR: 0.924, p = 0.509), despite its apparent protective association in the univariate model. Instead, the analysis highlighted factors reflective of aggressive disease biology and tumor burden as more influential on EFS outcomes. Membership in the R4 risk group (HR: 18.686, p = 0.002), elevated UA levels (HR: 5.953, p = 0.009), and LDH levels exceeding 1000 U/L (HR: 2.598, p = 0.039) were all significantly associated with increased risk of adverse events. Conversely, having a DLBCL subtype was linked to a significantly reduced risk of events (HR: 0.188, p = 0.017).

These findings suggest that while BMI may contribute to improved OS through its role in treatment tolerance and general health, its effect on recurrence or disease progression, as measured by EFS, is less pronounced than that of tumor-specific characteristics and risk classification. This aligns with prior observations in pediatric oncology, where laboratory markers such as LDH and clinical staging systems have shown greater predictive value for relapse and treatment failure than nutritional status alone [11,21]. Consequently, the integration of host-related factors like nutrition with tumor biology indicators may offer a more nuanced and comprehensive approach to prognosis and therapeutic decision-making.

In summary, our findings emphasize the heterogeneity in clinical behavior and outcomes among pediatric patients with high-risk mature B-cell lymphomas. Incorporating nutritional assessment alongside established clinical and laboratory variables could further enhance risk stratification and guide treatment optimization. Future research should continue to explore how nutritional status interacts with therapy response and disease biology, to improve individualized care and long-term outcomes in this aggressive lymphoma subtype.

Conclusion:

The present study demonstrates that nutritional status, as reflected by BMI, is an important predictive factor for clinical outcomes in pediatric patients with stage III and IV mature B-cell NHL. Patients with normal or higher BMI profiles tended to have higher complete response rates and lower mortality, suggesting a potential benefit of better nutritional status. This relationship underscores the potential benefit of integrating nutritional interventions and close BMI monitoring into risk stratification models for B-NHL.

Furthermore, our study suggests that enhanced supportive care measures to address malnutrition may improve treatment tolerability in these patients and ultimately contribute to better long-term outcomes. Future investigations should aim to elucidate the mechanisms by which BMI influences chemotherapy pharmacokinetics and immune response, thereby refining individualized therapeutic strategies for pediatric aggressive lymphomas.

List of Abbreviations

- B-NHL: B-cell non-Hodgkin lymphoma
- BFM: Berlin-Frankfurt-Münster
- BMI: Body Mass Index
- CBC: Complete Blood Count
- CNS: Central Nervous System
- CSF: Cerebrospinal fluid
- CR: Complete Response
- CT: Computed Tomography
- DLBCL: Diffuse Large B-Cell Lymphoma
- EFS: Event free survival
- LMB: Lymphoma- Malin de Burkitt
- LDH: Lactate Dehydrogenase
- MRI: Magnetic Resonance Imaging
- NHL: Non-Hodgkin Lymphoma
- OS: Overall survival
- PET: Positron Emission Tomography

- R2, R3, R4: Risk groups as defined by the BFM-95 protocol
- SECI: South Egypt Cancer Institute
- TdT: Terminal deoxynucleotidyl transferase
- UA: Uric Acid

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