






# Classification of Non-Hodgkin Lymphoma in Southeast Turkey: A Review of 550 Cases

## Güneydoğu Anadolu Bölgesindeki Non-Hodgkin Lenfoma Sınıflaması: 550 Hastanın İncelenmesi

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### Abstract

**Background:** The distribution of non-Hodgkin lymphoma (NHL) subtypes differs around the world. In this study we aimed to evaluate the gender, age, subtypes, biopsy sites, nodal and extranodal residential area, and stage of disease in the patients with NHL admitted to our hospital between January 2005 and December 2014.

**Materials and Methods:** The records of NHL patients admitted to our hospital between January 2005 and December 2014 were retrospectively reviewed

**Results:** Among 550 patients, 335 patients (60.9%) were male, 215 patients (39.1%) were female. The average age of over all the patients was 56 years (15-95). The average age of women was 57 (15-88), the average age of men was 54 years (15-95). The histological subtypes of NHL patients were as follows: 447 patients (81.3%) B-cell lymphoma, 84 patients (15.2%) T / NK cell lymphoma, 19 patients (3.5%) unclassified subtype. NHL patients divided into subtypes according to 2001 and 2008 WHO (World Health Organization) Classification and histopathologic subtypes were as follow: Diffuse Large B Cell Lymphoma (DLBCL) 295 patients (53.63%), small lymphocytic lymphoma (SLL) 37 patients (6.7%), Extranodal marginal zone lymphoma (MALT type) 37 patients (6.75%), peripheral T-cell Lymphoma 27 patients (4.9%), mantle cell lymphoma 26 patients (4.72%), Nodal Marginal Zone B-Cell Lymphoma 7 patients (1.3%), follicular lymphoma in 12 patients (2.1%), Burkitt's lymphoma 7 patients (1.3%), Splenic marginal zone B-cell lymphoma 4 patients (0.7). The most common subtype of NHL was DLBCL 295 patients (53.63%). Follicular lymphomas are less common in our center. Extranodal involvement rate was 38,5% of patients. According to the distribution of the sites of extranodal NHLs, the vast majority of patients 43% had GI tract involvement. The most commonly affected GI sites were stomach (27,8%). In this study 22.9% of the patients were in Stage 1, 26.7% in Stage 2, 19.5% in Stage 3, 30.9% in Stage 4 according to Ann- Arbor classification. In conclusion, the characteristics of NHLs in our region show some differences from other sites of the world.

**Conclusions:** The characteristics of NHL patients vary according to geographical differences. Present study has revealed the importance of geriatric assessment. NHL was observed frequently in men. Environmental risk factors have to research, epidemiologically. The most common subtype of NHL was DLBL. Follicular lymphomas are less common in our center. Improvement of national cancer registration system and multicenter large-scale studies reviewing the treatment protocols are needed to ensure the early diagnosis and therapy of NHL.

**Key words:** Non-Hodgkin's lymphoma; Epidemiology, Histological subtype, Extranodal involvement

### Öz

**Amaç:** Hodgkin olmayan lenfoma (NHL) alt tiplerinin dağılımı tüm dünyada farklılık gösterir. Bu çalışmada, Ocak 2005- Aralık 2014 tarihleri arasında hastanemize başvuran NHL hastalarında cinsiyet, yaş, alt tipler, biyopsi alanları, nodal ve ekstranodal yerleşim alanı ve hastalığın evrelerini değerlendirmeyi amaçladık.

**Materyal ve Metod:** Ocak 2005- Aralık 2014 tarihleri arasında hastanemize başvuran NHL hastalarının dosyaları retrospektif olarak tarandı.

**Bulgular:** 550 hastanın 335'i (%60,9) erkek, 215'i (%39,1) kadındı. Tüm hastaların üzerinde yaş ortalaması 56 idi (15-95). Kadınların yaş ortalaması 57 (15-88), erkeklerin yaş ortalaması 54 (15-95) idi. NHL hastalarının histolojik alt tipleri şu şekildedir: 447 hasta (%81,3) B hücreli lenfoma, 84 hasta (%15,2) T / NK hücre lenfoması, 19 hasta (% 3,5) sınıflandırılmamış alt tip. NHL hastaları 2001 ve 2008 WHO (Dünya Sağlık Örgütü) Sınıflandırmasına ve histopatolojik alt tiplerine göre alt tiplere ayrıldı: Diffüz Büyük B Hücreli Lenfoma (DLBCL) 295 hasta (% 53,63), küçük lenfositik lenfoma (SLL) 37 hasta (% 6,7), Ekstranodal marjinal bölge lenfoması (MALT tipi) 37 hasta (% 6,75), periferik T hücreli Lenfoma 27 hasta (% 4,9), manto hücreli lenfoma 26 hasta (% 4,72), Nodal Marjinal Bölge B-Hücre Lenfoması 7 hasta (% 1,3), 12 hastada foliküler lenfoma (% 2,1), Burkitt lenfoma 7 hasta (% 1,3), Splenik marjinal bölge B hücreli lenfoma 4 hasta (0,7). NHL'nin en sık görülen alt tipi DLBCL 295 hastayı (%53,63). Foliküler lenfomalar merkezimizde daha az görülür. Ekstranodal involvement oranı hastaların%38,5'i idi. Ekstranodal NHL'lerin bölgelerinin dağılımına göre, hastaların%43'ünde GI kanal tutulumu vardı. En sık etkilenen GI bölgeleri mide idi (%27,8). Bu çalışmada, hastaların %22,9'u Evre 1, Evre 2'de%26,7, Evre 3'te%19,5, Ann-Arbor sınıflandırmasına göre Evre 4'te%30,9 idi.

**Sonuç:** NHL hastalarının özellikleri coğrafi farklılıklara göre değişmektedir. Bu çalışma geriatric değerlendirmenin önemini ortaya koydu. NHL erkeklerde daha sık görüldü. Çevresel risk faktörleri epidemiolojik olarak araştırılmalıdır. NHL'nin en yaygın alt tipi DLBL'dir. Foliküler lenfomalar merkezimizde daha az görülür. Ulusal kanser kayıt sisteminin iyileştirilmesi ve NHL'nin erken tanı ve tedavisini sağlamak için tedavi protokollerini gözden geçiren çok merkezli büyük ölçekli çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Non-Hodgkin Lenfoma, Epidemiyoloji, Histolojik alttip, Extranodal tutulum

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## Introduction

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of malignancies arising from lymphoid tissue, with varied clinical and biological features (1). NHLs are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) cells. In the United States, B-cell lymphomas are diagnosed in 80% to 85% of people with 15% to 20% being T-cell lymphomas. NK-cell lymphomas are very rare. NHL is the sixth most common type of cancer according to the American Cancer Society, with about 71,850 cases diagnosed in 2015, 19,790 deaths, and 5-year relative survival of 71% (2).

NHL is the most common hematological malignancy and is currently classified according to the 2008 World Health Organization classification, which stresses the importance of integrating morphologic, immunophenotypic, molecular, cytogenetic and clinical findings in order to diagnose and properly classify lymphomas (3)

In all cases of NHL, the most important first step is an accurate pathologic diagnosis. The incidence of NHL varies significantly around the world, but few systematic, comparative studies of NHL subtypes by geographic region have been carried out (4-5). Notable increases in the incidence of NHL have been documented internationally throughout the second half of the twentieth century. Mortality rates from NHL also have increased, suggesting that changes in NHL classification alone cannot account for increasing rates (6-7). Although studies have identified etiologic factors that may have contributed to increasing NHL rates, such as viruses, medical conditions, drugs, and occupational or environmental exposures (8), most of the increase in NHL rates remains unexplained (9). For these reasons, NHL is a serious disease worldwide. In current study we aimed to evaluate the gender, age, subtypes, biopsy sites, nodal and extranodal residential area, and stage of disease in the patients with NHLs admitted to our hospital between January 2005 and December 2014, retrospectively

## Materials and Methods

All cases of NHL registered in the department of Hematology of Dicle University, Faculty of Medicine, between 2005 and 2014 were included in the analysis. This study protocol was approved by the local Ethics Committee, in accordance with the ethical principles for human investigations, as outlined by the Second Declaration of Helsinki. The patients were assessed with regard to their characteristics including age, gender, histological distribution, stage, extranodal involvement, presenting symptoms, and biopsied site. Diagnosis of NHL was made on the basis of morphologic evaluation, immunophenotypic, molecular, cytogenetic of lymph node tissue or extranodal tissue biopsy specimen. The term extranodal involvement indicates

either primary involvement or a manifestation of extensively disseminated systemic disease. Extranodal involvements were confirmed histologically and/or cytologically. Diagnosed before 2008 patients were classified according to the World Health Organization Classification (WHO) 2001(10) and diagnosed after 2008 were classified according to the World Health Organization Classification(WHO) 2008 (3).

Presenting symptoms of the patients were recorded. Extranodal NHLs were classified according to the involved organs. In this study, fever more than 38 degrees, night sweats, loss of body weight of more than 10% in the last 6 months were identified as B symptoms (11).

## Statistical analysis

All statistical analyses were performed using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL, USA). Clinical data of all patients including gender, age, lesion location, pathological type, and clinical stage were counted or measured. The proportions or the averages were used for processing and analysis.

## Results

Among 550 patients, 335 patients (60.9%) were male, 215 patients (39.1%) were female. The average age of over all the patients was 56 years (15-95). The average age of women was 57 (15-88), the average age of men was 54 years (15-95).

**Table 1.** The characteristics of the patients with NHL

Patients	N:550	Percentage %
Male	335	60,9%
Female	215	39,1%
Average age	56	(15-95)
<b>Cellular origin</b>		
B-cell lymphoma	447	81,3%
T -cell lymphoma	84	15,2%
Unclassified subtype	19	3,5%
<b>Stage (Ann- Arbor)</b>		
Stage 1	126	22,9%
Stage 2	147	26,7%
Stage 3	107	19,5%
Stage 4	170	30,9%
<b>Diagnostic biopsy region</b>		
Lymph node and intra-abdominal mass	214	38,9%
Superficial Lymph Node	197	35,8%
All other lymphoid regions	139	25,3%
Extranodal involvement	212	38,5%
<b>Complaints of the patients</b>		
Weakness and Fatigue	350	63%
Gastrointestinal Complaints	315	57%
B symptoms (night sweats, fever, weight loss)	240	43%
Painless peripheral lymphadenopathy	112	20%

The histological subtypes of NHL patients were as follows: 447 patients (81.3%) B-cell lymphoma, 84 patients (15.2%) T/NK cell lymphoma, 19 patients (3.5%) unclassified subtype. The characteristics of the patients were shown in Table 1. NHL patients divided into subtypes according to 2001 and 2008 WHO classification and the most common histopathologic subtypes were as follow: Diffuse large B

cell lymphoma (DLBCL) 295 patients (53,63%), small lymphocytic lymphoma (SLL) 37 patients (6.7%), Extranodal marginal zone lymphoma (MALT type) 37 patients (6,75%), peripheral T-cell Lymphoma 27 patients (4.9%), mantle cell lymphoma 26 patients (4.72%), nodal marginal zone B-cell Lymphoma 7 patients (1,3%), follicular lymphoma in 12 patients (2.1%), Splenic marginal zone B-cell lymphoma 4 patients (0,7), Burkitt's lymphoma 7 patients (1.3%).

**Table 2.** Distribution of patients according to the WHO histopathologic classification

	Patients (n)	Percentage(%)
<b>Mature B-cell NHL Subtypes</b>		
Diffuse Large B Cell Lymphoma	295	53,63
Chronic lymphocytic leukemia/Small Lymphocytic Lymphoma	37	6,7
Burkitt's Lymphoma	7	1,3
Hairy cell leukemia	9	1,6
Follicular Lymphoma Grade 1	5	0,9
Follicular Lymphoma Grade 2	3	0,55
Follicular Lymphoma Grade 3	4	0,7
Lymphoplasmacytic lymphoma	10	1,8
Extranodal marginal zone lymphoma (MALT type)	37	6,75
Mantle Cell Lymphoma	26	4,72
Nodal Marginal Zone B-Cell Lymphoma	7	1,3
Splenic marginal zone B-cell lymphoma	4	0,7
Primary mediastinal large B cell lymphoma	3	0,55
<b>T / NK-cell subtype of NHL</b>		
Peripheral T-Cell Lymphoma,NOS	27	4,9
Anaplastic Large T-Cell Lymphoma	24	4,4
Angioimmunoblastic Type Lymphoma	9	1,65
Precursor T-lymphoblastic leukaemia/lymphoma	6	1,1
Enteropathy-associated T-cell lymphoma	6	1,1
Primer Cutaneous T-Cell Lymphoma	6	1,1
ExtranodalNK / T cell lymphoma,nasal type	6	1,1
<b>Unclassified NHL</b>	<b>19</b>	<b>3,5</b>
<b>Total</b>	<b>550</b>	<b>%100</b>

The distribution of patients according to the WHO histological classification was shown in (Table 2). Out of the NHL patients, 212 patients (38.5%) had extranodal sites involvement. The most commonly involved regions were stomach in 59 patients (27.8%), Waldayer's ring 37 patients (17.4%), bone marrow 34 patients (16%). Extranodal of involvement regions of the patients were shown in Table 3.

## Discussion

The relative frequencies of NHL subtypes are different in various geographic regions of the World (4). The incidence of NHL is increasing all over the world. The incidence of NHL varies according to the age, geographic region, exposure to infectious agents, racial factor (2). In this study we evaluated 550 cases of NHL from South of Turkey, B-cell NHL was more frequent than T-cell NHL (Table 1). The most common lymphoma out and away was DLBCL (53.63%), followed by extranodal marginal zone lymphoma (MALT type) (6,75%). It has been shown that NHL is more

common in men than women in the studies (12-13). Male-to-female ratio was found to be 1.2 in Algeria,(14) , 0.94 in Romania (15). In a large-scale study evaluating incidence, survival and prevalence estimates for >20 subtypes of lymphoma showed that most subtype estimates being significantly higher in males than females (13).

**Table 3.** Extranodal of involvement regions of the patients.

Patients with Extranodal involvement	Number of the patients (n=212)	100 %
Gastrointestinal system involvement	92	43%
Stomach	59	27,8%
Waldayer Ring	37	17,4%
Bone marrow	34	16%
Bone	22	10,3%
Small intestine	21	10%
Central Nervous System	9	4,2%
Skin	9	4,2%
Colon-rectum	7	3,3%
Liver	5	2,3%
Testis	2	0,9%
Pleural-peritoneal involvement	2	0,9%
Liver	5	2,3%
All Other Regions	5	2,3%

In a study reported in our center in 2004, a total of 490 patients diagnosed histologically with NHL and of them 314 (64%) were men and 176 (36%) women and the male:female ratio was found to be 1.78 (16). In present study NHL was more common in men than women. Our center is a large center located in South east of Turkey which deals with most of the people farming. The farming is common among the men and an important income source in our region. The reason of frequency of NHL in men in our study may be exposure of the men to some chemical agents. Because, the studies have been showed that the risk of NHL was statistically significantly increased by exposure to the herbicides 2,4-dichlorophenoxyacetic acid, mecoprop and dicamba, insecticides malathion, 1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane (DDT), carbaryl, aldrin, and lindane; and to the fungicides captan and sulfur compounds (17). A multicentre prospective cohort study (EPIC) investigated occupational risks for lymphomas and they found a higher risk of NHL among car repair workers and butchers and a higher risk of HL among gasoline station workers suggest a possible role from occupationally related exposures, such as solvents and zoonotic viruses, as risk factors for malignant lymphoma (18). On the other hand there is a large petroleum refinery in Batman city neighboring to Diyarbakır. Ramis R. et al designed an analysis of matched geographical areas to examine NHL mortality in the vicinity of the 10 refineries sited in Spain over the period 1997-2006 and they concluded a possible increased risk of NHL mortality among populations residing in the vicinity of refineries (19). We suggested that studies are needed to assess the relationship between NHL and petroleum refinery.

Previous study conducted in our centre reported that the median age was 43 years (range: 14–90 years) in NHL patients (16). The median age was found to be 54 years in Algeria (14) and 57 years in Romania (15). In our study the average age of over all the patients was 56 years and 42% of patients were found to be over 60 years of age. Compared with South-eastern Europe (SEEU), it was determined that NHL was slightly higher (median 59,5 years) than our study whereas Western Europe (WEU) and North America (NA) were significantly higher (64 and 68 years, respectively) (4-20). On the other hand we suggested that hematological approach has gained importance in the geriatric population in our center.

**Table 4.** Frequencies of NHL subtypes by country and region

B-cell neoplasms	Southeast Turkey (current study) % (N)	South-eastern Europe % (N)	Western Europe % (N)	North America % (N)
Diffuse large B-cell lymphoma	53,65(295)	39,0 (232)	29,3 (170)	28,3 (113)
Marginal zone B-cell lymphoma, MALT type	6,75(37)	6,6 (39)	10,5 (61)	6,3 (25)
Follicular lymphoma, all grades	2,15(12)	15,8 (94)	20,0 (116)	33,6 (134)
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	6,7 (37)	11,3 (67)	8,6 (50)	4,8 (19)
Mantle cell lymphoma	4,72 (26)	5,9 (35)	8,3 (48)	7,0 (28)
Burkitt lymphoma	1,3 (7)	1,5 (9)	0,9 (5)	0,8 (3)
Marginal zone lymphoma, nodal/splenic	2 (11)	3,7 (22)	3,8 (22)	1,8 (7)
Primary mediastinal large B cell lymphoma	0,55(3)	2,4 (14)	2,9 (17)	1,0 (4)
Precursor B-cell lymphoblastic leukaemia/lymphoma	0,0(0)	0,7 (4)	0,2 (1)	0,5 (2)
High-grade B-cell lymphoma, Burkitt-like	0,0(0)	0,3 (2)	2,4 (14)	2,5 (10)
Plasmacytoma	0,0(0)	1,7 (10)	0,7 (4)	0,0 (0)
Lymphoplasmacytic lymphoma	1,8(10)	0,5 (3)	1,4 (8)	1,5 (6)
Hairy cell leukemia	1,6(9)			
Unclassifiable low-grade B-cell lymphoma	0,0(0)	1,2 (7)	1,2 (7)	1,3 (5)
Unclassifiable high-grade B-cell lymphoma	0,0(0)	0,7 (4)	0,7 (4)	1,3 (5)
Subtotal	81,3( 447)	91,1 (542)	90,9 (527)	90,5 (361)
<b>T-cell neoplasms</b>				
Peripheral T-cell lymphomas	4,9(27)	5,9 (35)	7,6 (44)	5,3 (21)
Extranodal NK/T-cell lymphoma, nasal type	1,1(6)	0,8 (5)	0,5 (3)	0,0 (0)
Precursor T-lymphoblastic leukaemia/lymphoma	1,1(6)	1,5 (9)	0,9 (5)	2,0 (8)
Mycosis fungoides	1,1(6)	0,7 (4)	0,2 (1)	2,3 (9)
Enteropathy-associated T-cell lymphoma	1,1(6)	0,0(0)	0,0(0)	0,0(0)
Anaplastic Large T-Cell Lymphoma	4,4(24)	0,0(0)	0,0(0)	0,0(0)
Angioimmunoblastic type Lymphoma	1,65(9)	0,0(0)	0,0(0)	0,0(0)
Subtotal	15,2(84)	8,9 (53)	9,1 (53)	9,5 (38)
<b>Unclassified NHL</b>	3,5(19)	0,0(0)	0,0(0)	0,0(0)
<b>Total</b>	<b>550</b>	<b>595</b>	<b>580</b>	<b>399</b>

In our study 22.9% of the patients were in Stage 1, 26.7% in Stage 2, 19.5% in Stage 3, 30.9% in Stage 4 according to Ann- Arbor classification. In previous study of our center, stages I,II, III, and IV were found in 67 (13.6%), 160 (32.7%), 171 (35%), and 92 (18.7%) of 490 patients, respectively (16). Boudjerra N et al. found that the majority of patients (60%) presented in advanced clinical stage (III or IV) (14). We suggested that early diagnosis had big importance for treatment of the patients. In the previous 15 years

of study at our university, in 36.7% of patients, the presence of B symptoms had been identified (16). In our study 43% of the patients had B symptoms.

**Table 5.** Distribution of the common NHL subtypes in the Mediterranean/Middle East

Common NHL subtypes	Southeast Turkey (current study)	Algeria (14)	Egypt [13]	Saudi Arabia [31]	Iraq [28]	Iran [29]	Kuwait [33]	Jordan [12]	Lebanon [27]	UAE [32]
Diffuse large B-cell lymphoma	53,65	52.8	31.0	49.8	54.6	37.8	49.1	36.0	40.4	59.0
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	6,7	12.2	6.0	6.8	5.8	23.9	10.2	3.7	3.8	1.0
Mantle cell lymphoma	4,72	2.5	5.9	1.6	1.9	2.2	1.4	6.3	6.0	NR
Follicular lymphoma, all grades	2,15	13.2	22.0	5.9	2.9	1.4	15.2	19.8	20.2	7.0
Extranodal NK/T-cell lymphoma, nasal type	1,1	3.0	NR	0.8	NR	NR	NR	1.1	0.5	NR
T-cell lymphomas, all subtypes	15,2	9.7	5.8	18.3	9.3	4.2	18.0	16.5	8.7	17.1

UAE, United Arab Emirates; NR, not recorded

The distribution of the sites of extranodal NHLs also differs in various geographic areas. The gastrointestinal tract (GI) and Waldeyer's ring were the major sites worldwide (21-22). Generally, the stomach was the most frequent site followed by the small bowel and colon in gastrointestinal tract lymphomas (23, 24). In previous study of our center Isikdogan et al found extranodal involvement in 44.5% of 218 NHL patients and the vast majority of patients (69.3%) had GI involvement and the most commonly affected GI sites was small bowel. (16). In current study extranodal involvement rate was 38,5% of patients. According to the distribution of the sites of extranodal NHLs, the vast majority of patients 43% had GI tract involvement. The most commonly affected GI sites were stomach (27,8%). According to previously published reports, the stomach was the most

commonly affected organ in other sites of Turkey (25-27). We suggested that with the widespread use of advanced imaging and histopathological diagnostic methods, detection of extranodal involvement became easier in recent years.

We compared the worldwide distribution of NHL subtypes (Table-5). Overall, the B-cell lymphoma accounted for a high proportion worldwide, the T-cell lymphoma in Asia was however higher than that in European and American countries. DLBCL is the pathological subtype with the highest rate of incidence all around the world, accounting for 30%-50% of NHL. DLBCL(53.63%) to be significantly higher in our study compared with South-eastern Europe (SEEU) (39%), Western Europe (WEU) (29,3%) and North America (NA) (28,3%), also FL(2,15%) was less common in our study than in SEEU (15,8%), WEU (20%) and NA (33,6%) (4,20) (Table 4), which is similar to the results reported from Mediterranean/Middle East countries such as Iraq and Iran, which are neighbor Souteast Turkey (28,29) (Table 5) On the other hand distribution of NHL subtypes differs between the regions. Previous studies have shown that FL is less common in Asia compared to Western world and other developing countries (30). Socioeconomic and environmental risk factors may play role in the etiology of FL.

T-cell lymphomas (especially PTL, NK/T, and T-LBL) in European and American countries were significantly lower than that in Asia. High frequencies of NK/T-cell lymphoma have been reported in Asian countries (30). In our study the rate of T-cell lymphomas(all types) (15,6%) were significantly higher compared with SEEU (8,9%) ,WEU (9,1%) and NA (9,5%) (20) and lower than China (30%) (30), Saudi Arabia (18,3%) (31) and United Arab Emirates (UAE) (17,1% )(32). T-cell lymphomas are aggressive lymphomas are difficult to treat. We suggested that studies are needed to investigate the risk factor of about this topic. As a result, the characteristics of NHL patients vary according to geographical differences. Present study has revealed the importance of geriatric assessment. NHL was observed frequently in men. Environmental risk factors have to research, epidemiologically. The most common subtype of NHL was DLBL. Follicular lymphomas are less common in our center. Improvement of national cancer registration system and multicenter large-scale studies reviewing the treatment protocols are needed to ensure the early diagnosis and therapy of NHL.

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