Original Article

Comparison of Survival Times of Diffuse Large B-Cell Lymphoma Patients with or without Gastrointestinal Involvement

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma (NHL) in Thailand. The gastrointestinal (GI) tract is among the most common sites for extranodal NHL. Studies showed that GI involvement had distinct characteristics, but overall survival compared with non-GI involvement was controversial. Our study aims to determine the overall survival between GI and non-GI DLBCL patients.

Materials and Methods: Based on Songklanagarind Hospital's lymphoma registration database from 2008 to 2013. All patients ≥18 years with histologically confirmed DLBCL were retrospectively reviewed. Exclusion criteria were primary CNS/mediastinal lymphoma, coexisting with other malignancies, and who received treatment before the study period. Baseline clinical characteristics, treatment response, and overall survival were obtained and analyzed according to GI and non-GI involvement. Subgroups of primary and secondary GI DLBCL were categorized by Dawson's criteria.

Results: A total of 455 patients were eligible, 89.2% were non-GI DLBCL and 10.8% were GI DLBCL. GI DLBCL patients had a lower hemoglobin level. The median survival of non-GI and GI groups was comparable (20.6 vs. 22.6 months). Among GI DLBCL, 73.5% were in secondary group. Primary GI DLBCL patients had a higher age, lower Ann Arbor staging, and a lower LDH level compared with the secondary group. The median survival of the primary group was insignificantly better than secondary group (73.4 vs. 13.3 months, *p*-value = 0.095).

Conclusion: Overall GI involvement in DLBCL patients was not correlated with poorer overall survival. But among GI DLBCL patients, primary GI DLBCL had distinct clinical characteristics and tended to have better survival than the secondary group.

Keywords: Diffuse large B-cell lymphoma, Gastrointestinal, Hodgkin's lymphoma, Lymphoma, Survival

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Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL) subtype, accounting for approximately one-third of all cases[1]. The disease is a molecularly, clinically, and pathologically varied entity. The heterogeneity among DLBCL patients might reflect the wide variation in long-term outcomes as 5-year survival rates of such patients range from 30 to 80%. The most common prognostic tool that has been used in patients with DLBCL is the International Prognostic Index (IPI) score, which has shown to be useful in this post-rituximab era[2]. The factors included in the IPI score are age, stage of disease, performance status, number of extranodal sites, and lactate dehydrogenase (LDH) level[3]; a higher score is a prognostic predictor of poor outcome. Nonetheless, no primary extranodal site of involvement is included in this score.

Recent study reported that primary extranodal sites of lymphoma involvement are related with different outcomes in patients with DLBCL[4]. Approximately one-third of DLBCL have a primary extranodal origin[5]. Gastrointestinal (GI) tract is among the most common sites for NHL arising extranodally, accounting for 10 to 15% of NHL, 5 to 20% of all lymphoma, and 30 to 40% of primary extranodal lymphoma[6]. Furthermore, GI tract is the most common extranodal site of lymphoma involvement in an immunocompetent host[6] and the second most common extranodal site in an immunocompromised host, secondary to central nervous system DLBCL[7].

According to the type of GI involvement, there are 2 types of GI lymphoma: primary and secondary GI lymphoma. From the previous reports, primary GI lymphoma is very rare, the prevalence is only about 1 to 4% of all GI malignancies[8]. Dawson's criteria[9] are used to categorize primary GI lymphoma, including: (1) absence of peripheral lymphadenopathy at the time of presentation, (2) lack of enlarged mediastinal lymph nodes, (3) normal total

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and differential white blood cell count, (4) predominance of bowel lesion at the time of laparotomy with only lymph nodes obviously affected in the immediate vicinity, (5) no lymphomatous involvement of liver and spleen.

A study by Lopez-Guillermo[10] noted that gastrointestinal DLBCL showed a significantly better 5-year overall survival than all DLBCL. In contrast, a study by Castillo[4] noted that sites of involvement associated with worse overall survival were GI DLBCL. In Thailand, the prevalence of GI DLBCL is rarely reported. It constituted from 4.8% to 8.5% of all NHLs[11,12]. There was a previous study focused on GI involvement in lymphoma in Thailand, but not limited to DLBCL, which noted that there are different characteristics between primary and secondary GI lymphoma[13], but overall survival compared with non-GI involvement were controversial. Moreover, no previous study in Thailand focused on the difference in overall survival of DLBCL according to GI involvement.

The main objective of our study is to determine the overall survival between adult GI and non-GI DLBCL over a 7-year period at Songklanagarind Hospital. The secondary objectives are to study the demographic, clinical characteristics, and overall survival of the patients with primary GI DLBCL compared to secondary GI DLBCL.

Materials and Methods

Study population

Based on Songklanagarind Hospital's lymphoma registration database of the Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University between October 2008 and October 2013. Patients with histologically proven diffuse large B-cell lymphoma with the International Classification of Diseases 10 code C833 (diffuse non-Hodgkin's lymphoma-Large cell [diffuse]) and age of at least 18 years were retrospectively reviewed. Exclusion criteria were (1) chemotherapy/radiotherapy treatment before the study period, (2) diagnosis of relapsed DLBCL, (3) primary site of the lymphoma was central nervous system (CNS) or mediastinum, and (4) coexisting other malignancy.

All eligible patients' data were retrospectively reviewed. The baseline clinical and laboratory characteristics data were collected, including, but not limited to, age at diagnosis, year of diagnosis, gender, performance status, Ann Arbor staging, complete blood count (CBC), lactate dehydrogenase level (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level. Treatment response data were also retrieved from the registration database. The survival time data were retrieved from the lymphoma registration database, the medical records, and Thailand's civil registration database.

The present study was approved by the Institutional Review Board of the Faculty of Medicine, Prince of Songkla University, Thailand.

Definition of variables

Baseline lymphoma stage in this study was divided into early (Ann Arbor Stage I/II) and advanced (III/IV). GI site of involvement was categorized into 4 major sites: stomach, pancreas, small intestine, and large intestine. Dawson's criteria[8], as mentioned earlier, were used to sub-categorize patients with GI involvement into primary and secondary GI DLBCL. Overall survival was the outcome of interest. For the patients who were not undergo laparotomy, the bowel lesion, as well as intraabdominal lymph node(s), liver, and spleen involvement data were retrieved from imaging (ultrasonography or computed tomography of abdomen) reports and medical records. Overall survival was calculated as the time (in months) elapsed between the date of diagnosis and the date of death, date of last known as alive status, or date of the study cutoff.

Statistical analysis

Continuous data are presented as mean with standard deviation (SD), or median with IQR according to the distribution of observed value differences in data using the Student t-test. Categorical data are presented as number and percentage, and differences in data using the Chi-square test or Fisher's exact test. Overall survival estimates were calculated using the Kaplan-Meier method. Calculations and graph were obtained using R program.

Results

Characteristics of the population

Our study included patients with a diagnosis of lymphoma with the International Classification of Diseases 10 code C833 (diffuse non-Hodgkin's lymphoma-large cell [diffuse]) in the registration database made between October 2008 and October 2013 at Songklanagarind Hospital (n = 478). We excluded patients with primary CNS DLBCL (n = 14), coexisting other malignancies (n = 7), previous treatment (n = 1), and no histological confirmation (n = 1). Primary CNS DLBCL was excluded as the characteristics and outcomes of those cases are distinct and have no defined staging system. Our final study population included 455 individuals. There were 406 cases of non-GI DLBCL and 49 cases (10.8%) of GI involvement (Figure 1). Of the 49 DLBCL cases with GI involvement, 89.8% were histologically proven at the site of GI involvement, and 10.2% were diagnosed by imaging while the tissue was obtained from other sites.

The GI sites of involvement included stomach (16 cases, 32.7%), pancreas (1 case, 2.0%), small intestine (14 cases, 28.6%) and large intestine (14 cases, 28.6%). There were some cases with multiple sites of GI involvement (4 cases, 8.16%). According to the type of GI involvement, there were 13 cases of primary GI DLBCL (primary group) and 36 cases of secondary GI DLBCL (secondary group) according to Dawson's criteria (Figure 1).

Characteristics of the population according to the presence of GI involvement

All comparisons were made between DLBCL patients with and without GI involvement. There were no

significant differences of demographic data and clinical characteristics at the time of diagnosis between non-GI and GI DLBCL, except for hemoglobin (Hb) level; lower baseline Hb level was observed in the GI DLBCL group (Table 1). There was male predominance, high Ann Arbor stage (III to IV) and low ECOG (1 to 2) in the majority of both groups.

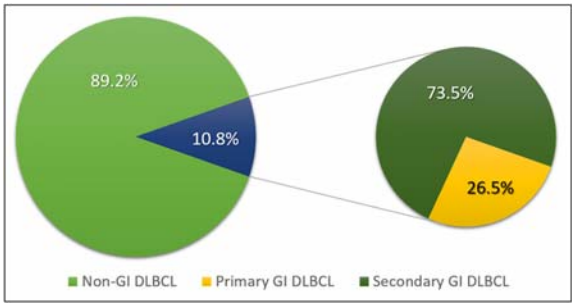

Figure 1. Proportion of diffuse large B-cell lymphoma (DLBCL) patients with and without gastrointestinal (GI) involvement, and subcategorized into primary and secondary GI DLBCL according to Dawson's criteria.

The median LDH level and white blood cell (WBC) count were insignificantly higher in non-GI DLBCL than GI DLBCL. About three-fourth of patients in both groups received treatment; the type of treatment and the treatment outcomes (CR, PR) were similar, except for the higher proportion of GI DLBCL underwent surgery (Table 1).

Characteristics of the GI DLBCL population according to primary and secondary GI involvement

Among subgroups of patients with GI involvement, there were some differences in baseline characteristics between primary and secondary GI DLBCL patients (Table 2). The mean age at diagnosis was significantly higher in primary than secondary GI DLBCL. The majority of primary GI DLBCL patients were in early Ann Arbor staging, but a higher proportion of advanced disease stage was observed in the secondary GI DLBCL group. The performance status was significantly better in the primary than the secondary group. Based on baseline laboratory data, there was a significantly lower median LDH level in the primary than in the secondary group. Other baseline characteristics were comparable in both groups. The proportion of patients who underwent treatment and the treatment outcome were also similar between the primary and the secondary group, patients with primary GI DLBCL were more likely to receive rituximab

Table 1. Baseline demographic data, clinical characteristics and treatment outcome of 455 DLBCL patients according to GI involvement

Characteristics	No GI involvement (n = 406)	GI involvement (n = 49)	*p*-value
Age, median (IQR)	57.8 (45.6, 69.4)	54.2 (44, 62.9)	0.110
Male gender, n (%)	235 (57.9)	35 (71.4)	0.095
Ann Arbor stage, n (%)			0.159
I to II	154 (37.9)	13 (26.5)	
III to IV	252 (62.1)	36 (73.5)	
ECOG, n (%)			0.464
1 to 2	359 (88.4)	41 (83.7)	
3 to 4	47 (11.6)	8 (16.3)	
Positive anti-HIV, n (%)	27 (6.6)	6 (12.2)	0.148
LDH (U/L), median (IQR)	651 (395, 1,346)	596 (387, 999)	0.370
WBC (cells/mm^3), median (IQR)	7,430 (5,482, 9,555)	6,750 (5,130, 9,430)	0.475
Hemoglobin (g/dL), median (IQR)	11.2 (9.4, 12.8)	9.7 (8.4, 11.5)	0.002
Platelet (/mm^3), median (IQR)	257,000 (191,000, 350,750)	287,000 (240,000, 341,000)	0.090
AST (U/L), median (IQR)	26 (20, 44)	24 (19, 41)	0.247
ALP (U/L), median (IQR)	93 (73, 148)	93 (78, 148)	0.518
Treatment, n (%)	305 (74.6)	36 (73.5)	1
Rituximab	78 (19.1)	12 (24.5)	0.477
Chemotherapy	303 (74.1)	38 (77.6)	0.724
Radiation	60 (14.8)	5 (10.2)	0.517
Surgery	0	5 (10.2)	<0.001
Treatment outcome, n (%)			0.556
CR and PR	204 (67.5)	22 (61.1)	
SD and PD	98 (32.5)	14 (38.9)	

DLBCL = diffuse large B-cell lymphoma, GI = gastrointestinal, IQR = interquartile range, n = number, ECOG = Eastern Cooperative Oncology Group Performance status, HIV = Human Immunodeficiency Virus, LDH = lactate dehydrogenase, WBC = white blood cells, AST = aspartate aminotransferase, ALP = alkaline phosphatase, CR = complete remission, PR = partial remission, SD = stable disease, PD = progressive disease

therapy than secondary GI DLBCL, but the statistically significant level was not reached (Table 2).

Survival analysis of patients with DLBCL according to GI involvement

The median overall survival of patients without GI involvement was 20.6 months, and median overall survival of GI DLBCL was 22.6 months (Figure 2). The Kaplan Meier plot shows no statistically significant differences in overall survival between non-GI and GI DLBCL ($p = 0.109$).

Survival analysis of patients with DLBCL according to the type of GI involvement

Among patients with GI involvement, the median overall survival of primary GI DLBCL was 73.4 months, and the median overall survival of secondary GI DLBCL was 13.3 months (Figure 3). The Kaplan Meier plot shows no significant differences in overall survival between the primary and the secondary GI DLBCL group ($p = 0.095$).

Discussion

This is the first study in Thailand evaluating the presence of GI involvement as a prognostic role on survival in patients with DLBCL. In such case, Songklanagarind Hospital's lymphoma registration database provides a real-world setting that facilitates the study of the association between GI involvement and clinical characteristics, and survival of DLBCL patients. Our study demonstrates that the presence of overall GI involvement is not associated with a worse prognosis than general DLBCL patients.

The prevalence of GI DLBCL in this retrospective study was 10.8%, which is similar to previous studies[4,10]. The baseline characteristics of GI DLBCL patients in our study were male predominance and advanced clinical staging at diagnosis corresponding to previous observation[4], whereas the other study[10] found early clinical staging at diagnosis.

In the present study, we found some distinct baseline characteristics according to GI involvement in DLBCL patients. Firstly, a lower hemoglobin level at diagnosis was observed in GI DLBCL group. This result could be explained

Table 2. Baseline demographic data, clinical characteristics and treatment outcome between primary and secondary GI DLBCL patients

Characteristics	Primary GI DLBCL (n = 13)	Secondary GI DLBCL (n = 36)	*p*-value
Age (years), mean (SD)	61.6 (12.7)	50.5 (15.1)	0.023
Male gender, n (%)	8 (61.5)	27 (75.0)	0.476
Ann Arbor stage, n (%)			<0.001
I to II	13 (100.0)	0	
III to IV	0	36 (100.0)	
ECOG, n (%)			0.090
1 to 2	13 (100.0)	27 (77.8)	
3 to 4	0	8 (22.2)	
Positive anti-HIV, n (%)	0	6 (16.7)	0.175
LDH (U/L), median (IQR)	385.0 (350, 560)	699.5 (428, 1,182)	0.007
WBC (cells/mm^3), median (IQR)	5,710 (5,010, 7,190)	6,955 (5,427, 9,442)	0.234
Hemoglobin (g/dL), mean (SD)	10.3 (2.4)	9.9 (1.9)	0.502
Platelet (/mm^3), median (IQR)	255,000 (182,000, 306,000)	295,000 (240,000, 343,500)	0.221
AST (U/L), median (IQR)	25 (18, 41)	25 (19, 40)	0.692
ALP (U/L), median (IQR)	88 (74, 100)	102 (79.5, 185.5)	0.154
GI site of involvement, n (%)			0.301
Stomach	7 (53.8)	9 (25)	
Pancreas	0	1 (2.8)	
Small intestine	2 (15.4)	12 (33.3)	
Large intestine	4 (30.8)	10 (27.8)	
2 or more GI sites	0	4 (11.1)	
Treatment, n (%)	12 (92.3)	26 (72.2)	0.140
Rituximab	6 (46.2)	6 (16.7)	0.058
Chemotherapy	12 (92.3)	26 (72.2)	0.246
Radiation	1 (7.7)	4 (11.1)	1
Surgery	0	5 (13.9)	0.306
Treatment outcome, n (%)			0.292
CR and PR	9 (75)	13 (54.2)	
SD and PD	3 (25)	11 (45.8)	

GI = gastrointestinal, DLBCL = diffuse large B-cell lymphoma, SD = standard deviation, IQR = interquartile range, n = number, ECOG = Eastern Cooperative Oncology Group Performance status, HIV = human immunodeficiency virus, LDH = lactate dehydrogenase, WBC = white blood cells, AST = aspartate aminotransferase, ALP = alkaline phosphatase, CR = complete remission, PR = partial remission, SD = stable disease, PD = progressive disease

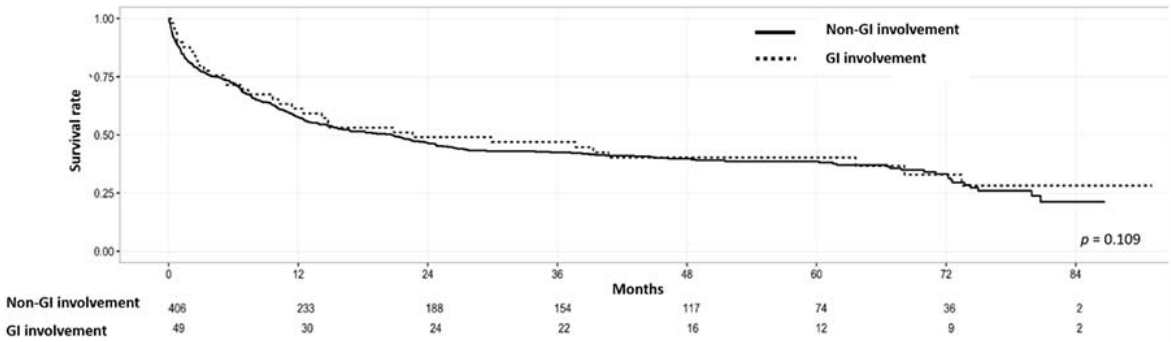

Figure 2. Overall survival of patients with diffuse large B-cell lymphoma (DLBCL) according to gastrointestinal involvement.

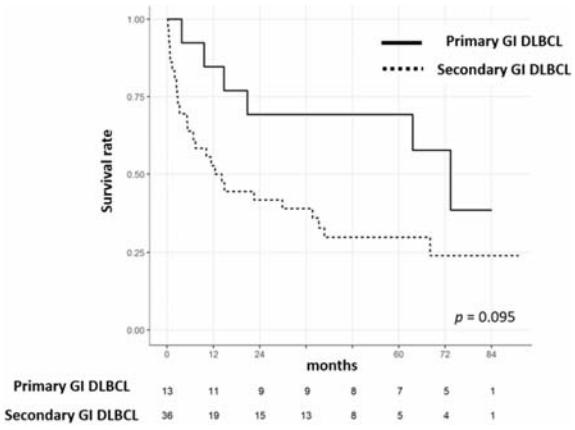

Figure 3. Comparison of overall survival between primary and secondary gastrointestinal diffuse large B-cell lymphoma (GI DLBCL).

by occult and overt GI bleeding in GI DLBCL as a possible cause of a lower baseline Hb level. Secondly, not all GI DLBCL patients are the same. Patients with primary GI DLBCL, despite a higher age at diagnosis, had lower Ann Arbor staging, and a lower baseline LDH level. Interestingly, we found that the majority of GI DLBCL was in the "secondary group" (73.5%), which was different from the previous study of GI lymphoma in Thailand. In Sukpanichnant's study[13], the prevalence of primary and secondary GI lymphoma in Thailand were 86.7% and 13.3%, respectively. Dissimilarities between our study and the previous GI study might be due to differences in research methodology. In Sukpanichnant's study, based on the pathological report of GI lymphoma from the Department of Pathology and then clinical data of the patients were subsequently reviewed, selection bias might have occurred. And all types of lymphoma, not only DLBCL, were included. In our study, we focused only on patients with DLBCL, based on lymphoma registration database, which included all baseline data and then confirmed histologically, which should reflect the real-world situation more accurately.

In survival analysis, our study showed no relationship between presence of GI involvement in DLBCL patients and overall survival. However, when we looked more deeply into the subgroups of patients with GI involvement, there was a trend toward better survival in primary GI DLBCL than in the secondary GI DLBCL group. Our finding is concordant with the previous research by Lopez-Guillermo[10], who studied patients with various primary organs of DLBCL, showing that GI DLBCLs presented with early-stage disease, and were associated with a better prognosis than all DLBCLs. But our data showed contradictory results when compared with Castillo's study[4], which was based on the SEER database including White, Hispanic and Black populations. Castillo noted that primary GI DLBCL was associated with poorer survival, despite the subset of early stage patients. Apart from race and ethnicity, which might have an impact on outcomes as mentioned by Castillo's group[4], the different methodologies of the studies may have played a role in the different results. Our study and Lopez-Guillermo's study are single center studies in which medical records and the clinical features of the patients were accessible for review, whereas in Castillo's study, using the SEER database, primary site of DLBCL was retrieved as were coded by ICD-O-3, which may not precisely reflect "true" primary GI DLBCL as defined by Dawson's criteria.

As mentioned earlier, among the subgroup of GI DLBCL patients, our study showed that the "primary group" had distinct clinical characteristics and tended to have better survival than the "secondary group". The better survival trend may be due to different baseline characteristics between the two groups. The "primary group" had a better performance status and was more likely to be in early stage than the "secondary group". Significantly higher LDH levels in the "secondary group" could also explain the result, as LDH level is one of the factors of IPI or NCCN-IPI scores that were commonly considered as a clinical predictive system for patients with DLBCL and limited stage of DLBCL, respectively[14,15].

The main limitations of our study are inherent to the nature of its design. First, it was a single center study;

thus, its results may not represent the whole Thai population well. Second, the sample size of patients with GI involvement, especially primary GI DLBCL, was relatively small. We may see a statistically significant survival advantage in primary GI DLBCL over secondary GI DLBCL in a study with a larger sample size. Third, because this was a retrospective study, some patients were lost to follow-up, but date of death data were also retrieved from the national civil's registration database making the survival data of the patients in our study more accurate. And lastly, some DLBCL may progress and transform from low-grade lymphomas such as marginal zone and follicular lymphoma, we did not have such data in our database, hence, whether this transformation has an impact on the overall survival among non-GI and GI DLBCL cannot be depicted in our study.

The present study also has its strength. First, it is the first study in Thailand assessing the prognostic role of GI involvement on survival in DLBCL patients; moreover, to our knowledge, this is the first study evaluating survival between primary and secondary GI DLBCL with an interesting result, although statistical significance was not reached. Further multi-center studies with larger sample sizes are needed in order to establish exact survival according to the type of GI DLBCL. Second, all patients in our study had histologically proven DLBCL, determined by central pathologists at Songklanagarind Hospital. The other strength was Songklanagarind's lymphoma registration database, which had complete data of all the baseline characteristics, treatment responses and outcomes despite being a retrospective study.

Conclusion

The present study described the clinical characteristics of GI involvement in patients with DLBCL which is the most common type of lymphoma found in Thailand. The overall survival for any DLBCL with GI involvement was not different from patients without GI involvement, but the subtype of GI involvement might have and impact on clinical outcomes, patients with primary GI DLBCL had much longer survival times than secondary GI DLBCL, however, the statistical significant level was not reached.

What is already known in this topic?

DLBCL is the most common NHL in Thailand. GI tract is the most common extranodal site of lymphoma involvement in an immunocompetent host and the second most common in an immunocompromised host. Studies showed that GI involvement had distinct characteristics, but overall survival compared with non-GI involvement were controversial.

What this study adds?

This is the first study in Thailand evaluating the presence of GI involvement as a prognostic role on survival in patients with DLBCL. The prevalence of GI DLBCL in Thailand was 10.8%, and most of them (73.5%) are "secondary involvement" of GI DLBCL. There is no relationship between presence of GI involvement in DLBCL patients and overall survival. However, when categorized into the subgroups of patients with GI involvement, there was a trend toward better survival in primary GI DLBCL than in the secondary GI DLBCL group (73.4 vs. 13.3 months).

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Potential conflicts of interest

The authors declare no conflicts of interest.

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