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No outcome disparities in patients with diffuse large B-cell lymphoma and a low socioeconomic status

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ABSTRACT

Introduction: In patients with diffuse large B-cell lymphoma (DLBCL) socioeconomic status (SES) is associated with outcome in several population-based studies. The aim of this study was to further investigate the existence of disparities in treatment and survival.
Methods: A population-based cohort study was performed including 343 consecutive patients with DLBCL, diagnosed between 2005 and 2012, in the North-west of the Netherlands. SES was based on the socioeconomic position within the Netherlands by use of postal code and categorized as low, intermediate or high. With multivariable logistic regression and Cox proportional hazard models the association between SES and respectively treatment and overall survival (OS) was evaluated.
Results: Two-third of patients was positioned in low SES. Irrespective of SES an equal proportion of patients received standard immunochemotherapy. SES was not a significant risk indicator for OS (intermediate versus low SES: hazard ratio (HR) 1.31 (95%CI 0.78–2.18); high versus low SES: HR 0.83 (95% CI 0.48–1.46)). The mortality risk remained significantly increased with higher age, advanced performance status, elevated LDH and presence of comorbidity.
Conclusion: Within the setting of free access to health care, in this cohort of patients with DLBCL no disparities in treatment and survival were seen in those with lower SES.

1. Introduction

The survival of patients with diffuse large B-cell lymphoma (DLBCL) has substantially improved since the introduction of rituximab, with an approximate 20% increase in 5-year overall survival (OS) in randomized controlled trials (RCT) [1]. This improvement in OS is also shown in an unselected DLBCL patient population from a large Dutch population-based cohort study [2]. In the rituximab-era, clinical prognostic factors that are incorporated in the International Prognostic Index (IPI) score are still valid to determine outcome of patients [3].

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Besides these 'classic' prognostic factors, several population-based studies report disparities in survival of non-Hodgkin lymphoma (NHL) patients with low socioeconomic status (SES), with more advanced disease at time of diagnosis [4], the presence of more comorbidity that may interfere with intensive treatment [5–8] and possible inequalities in treatment [9,10]. These associations may be explained by several social factors, including a delay in seeking medical advice, inadequate insurance coverage and inability to cover other contributing costs, resulting in inequalities in health care access [7,11,12]. However, information on the treatment given and whether standard immunochemotherapy was initiated and finalized is not thoroughly documented in previous studies. In the Netherlands, an insurance coverage is obligatory for all inhabitants since 2006. Although this provides in an equal access to health care services, it is not clear whether this equal access sufficiently provides in optimal treatment across all socioeconomic groups. Other factors, such as the presence of more comorbidity, may also interfere with optimal therapy in patients with low SES [12].

An observational, population-cohort study including a consecutive series of patients was designed to investigate the association between SES, treatment and outcome in the Netherlands, a country with equal health-care access. The aim was to examine if treatment disparities were present in the use of standard immunochemotherapy and whether socioeconomic disparities in outcome could be attributed to either the treatment given or to differences in other factors, such as the traditional prognostic factors and comorbidity.

2. Methods

2.1. Hemobase

Starting in 2005, all consecutive patients from the five medical centres in Friesland, a province in the Northern part of the Netherlands with 650,000 inhabitants, diagnosed with a hematological malignancy were prospectively registered in a clinical database, HemoBase, for objective assessment of clinical parameters and for research purpose. HemoBase is a web-based,

Table 1
Baseline characteristics and treatment of the 343 patients with DLBCL, diagnosed between 2005 and 2012, stratified for socioeconomic status.

	Total (N = 343)		High SES (N = 47)	Intermediate SES (N = 50)	Low SES (N = 232)
	N	%	%	%	%
Age					
<60	92	27	36	30	24
60–79	184	54	51	52	55
≥80	67	19	13	18	21
Median age (in years)		69	65	70	70,5
Gender					
male	178	52	57	48	51
Place of residence					
urban	114	33	36	40	33
rural	216	63	64	60	67
missing	13	4	–	–	–
Ann Arbor stage					
1	85	25	27	22	25
2–4	250	73	66	76	73
missing	8	2	7	2	2
Performance status					
0–1	265	77	60	82	79
≥2	66	19	31*	16	18
missing	12	4	9	2	3
IPI					
0–1	123	36	36	44	34
2	77	22	19	14	25
3	74	22	21	26	20
4–5	54	16	15	12	18
missing	15	4	9	4	3
CCI					
0–1	278	81	79	78	81
≥2	64	19	19	22	19
missing	1	–	2	–	–
Treatment					
standard ICT	293	85	85	86	85
other ICT	12	4	2	4	5
other supportive care	37	11	13	10	10
missing	1	–	–	–	–
Standard ICT completed	249	85	80	81	88
Radiotherapy	110	31	32	30	32

*Significant difference $p < 0.05$.
Abbreviations: LDH: lactate dehydrogenase; IPI: International Prognostic Index; SES: socioeconomic status at neighborhoodlevel classified as low, intermediate or high based on the 4-digit postal code; ICT: immunochemotherapy; Standard ICT: R-CHOP21 or R-CHOP14 (rituximab-cyclophosphamide, doxorubicin, vincristin and prednisone); n/a: not applicable.
SES data was missing for 14 patients.

multidisciplinary, population-based electronic health record specifically designed by professionals for the hemato-oncology. With direct registration by professionals involved in the diagnostic work-up and treatment, the database is representative for the incidence, characteristics and treatment of patients with a hematological malignancy in the complete Friesland area [13].

2.2. Study population

In the current study all consecutive patients at age ≥18 years diagnosed with DLBCL between 1 January 2005 until 31 December 2012 were included. Excluded were: patients (n = 77) with transformation from low-grade lymphoma into DLBCL, recurrent disease, cutaneous DLBCL, primary DLBCL of central nerve system and primary effusion lymphoma. To ensure that all diagnoses of DLBCL were captured, the HemoBase database was compared with the nationwide Netherlands Cancer Registry; no discrepancies were found. Approval was obtained from the Medical Ethics Review Committee from Medical Centre Leeuwarden for this observational study. Informed consent was waived in accordance with Dutch regulations.

2.3. Study variables

2.3.1. Patient- and disease characteristics

All relevant data of clinical characteristics and prognostic factors (Table 1) were retrieved from HemoBase and local patient records. Comorbidity data at time of diagnosis was collected retrospectively and scored by using the Charlson Comorbidity Index (CCI) [14]. To minimize the risk for incomplete data, the CCI of all patients were discussed with the treating clinicians. This way, we ensured the presented data is a correct reflection of the actual CCI. A high comorbidity score was defined as CCI ≥ 2 [8]. The International Prognostic Index (IPI) was calculated for every patient. The histological diagnoses were made on the first nodal or extranodal biopsy according to the World Health Organization classification [15]. Information about the degree of urbanization was obtained from "Statistics Netherlands (CBS)".

2.3.2. Treatment

Treatment was documented in all patients, and the main treatment modality was categorized in either standard immunochemotherapy, defined as R-CHOP21 or R-CHOP14, other (suboptimal) immunochemotherapeutic regimes or palliative treatment (supportive care or radiotherapy only). Of all patients who received immunochemotherapy, the number of cycles, the administration of granulocyte-colony stimulating factor (G-CSF) and the application of additional radiotherapy was documented.

2.3.3. SES

SES was defined on the level of neighborhood and at the level of district.

From 1998 neighborhood SES data are available for each four-digit postal code area with more than one hundred households and provided by the "Sociaal Cultureel Planbureau (SCP)", a governmental organization [16]. These neighborhood SES data are based on four parameters: (1) mean annual income per household, (2) the percentage of households with a low income, (3) proportion of households with low education level and (4) percentage of unemployment. These variables are used as a combined score and the data is updated every four years. To determine the socioeconomic position of a neighborhood within the Netherlands, the scores are ranked. Based on these rank numbers SES is divided into quintiles and categorized into three groups: high (first and second quintile), intermediate (third quintile) and low (fourth and fifth quintile) SES. Neighborhood SES based on postal code is widely used in previous Dutch studies [17–21] and the main analysis was performed with these data. To evaluate the impact of this definition of SES a second analysis was performed in which SES was defined at the level of quarters, which are smaller areas than the 4-digit postal code region. The quarter level SES is a combined score based on income level, degree of unemployment and percentage of house ownership and also categorized in high, intermediate and low SES [22].

2.4. Follow-up

Follow-up was completed until 01 July 2014. Tumor responses in patients who completed R-CHOP therapy were classified as complete remission (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the International Working Group [23]. Recurrent or progressive disease was documented, and treatment accordingly. Survival time (in months) was defined as the time period from date of diagnosis until date of death or date of last follow-up. In case of death, causality with disease or treatment was recorded.

2.5. Statistical analysis

For describing differences between SES groups Chi-square tests were used. The influence of SES on the initiation of standard immunochemotherapy and ability to complete treatment was evaluated by use of multivariable logistic regression models, with calculation of odds ratios (OR), corresponding 95% confidence intervals (95% CI) and adjustment for other predictors when applicable.

The following variables were evaluated as potential predictors for OS: gender, age, Ann-Arbor stage, presence of extranodal disease, performance status (PS), elevated lactate dehydrogenase (LDH), IPI, CCI, SES and place of residence. To identify the impact of these variables on OS the Cox proportional hazard modeling was used. Resulting risk estimates are presented as hazard ratios (HR) with related 95% CI. Within the multivariable analysis a backward strategy was used, starting with the full model in which variables significant at a P-value <0.10 with reduction to a final model ending with all variables at a level of $P < 0.05$. Given the aim of the study, SES remained included in the final model.

All analyses were performed using commercially available computer software (Statistical Analysis System version 9.3; SAS Institute, Cary, NC).

3. Results

343 patients with DLBCL were eligible for the study. The baseline characteristics are depicted in Table 1. Two-third of the patients was classified as low SES. SES data was missing in 14 patients. Comparing the SES subgroups, only performance status was significantly different at baseline, with more advanced performance status (PS ≥ 2) in patients with high SES (Chi-square P = 0.03).

Immunochemotherapy was initiated in 305 patients (89%) and the majority (85%) received the standard regime with either R-CHOP21 or R-CHOP14. Of those treated with standard immunochemotherapy, 85% of the patients completed treatment with either 6 or 8 cycles or in case of stage I disease 3 or 4 cycles followed by radiotherapy. Slightly more than one-third received G-SCF as supportive care during immunochemotherapy. Overall, 31% of the patients received radiotherapy with 3% as sole palliative treatment. In the other 28% (n = 98) of patients who received radiotherapy, 59% (n = 58) had stage I disease and 41% (n = 40) suffered from advanced disease without CR after immunochemotherapy. In 251 patients (82%) either CR or PR was documented during or after finalizing immunochemotherapy. In 75% of the

patients who received response evaluation (n = 270) a PET scan was performed. At the time of analysis 138 patients (40%) had died and the majority of deaths were disease-related (58%; Table 2).

As shown in Table 3, the likelihood to receive standard immunochemotherapy and the ability to complete treatment did not differ between patients with low, intermediate and high neighborhood SES. A decreasing odds ratio was seen in use of standard immunochemotherapy and the ability to complete treatment with increasing age, PS ≥ 2, and CCI ≥ 2.

The median duration of follow-up was 55 months (95% CI 48–58 months). Median survival time was 90 months for the whole population. The variables significantly increasing mortality risk are depicted in Table 4. At univariable analysis, the classic prognostic factors and place of residence were significantly associated with OS. As shown in Table 4, in the final multivariable Cox regression model that included SES, only age, PS ≥ 2, elevated LDH, and CCI ≥ 2 were independently associated with an increase in mortality risk. Neighborhood SES did not appear to be a significant risk indicator (Fig. 1).

With SES measured at district level, also no differences in standard and complete immunochemotherapy was seen between the three SES groups and it was not significantly associated with OS (data shown in Supplementary Table S5 and S6).

Table 2
Response evaluation and follow-up data of the patient cohort with DLBCL, diagnosed between 2005 and 2012.

	N	%
Response during/after ICT (305)		
CR	214	70
PR	37	12
SD	6	2
PD	13	5
n/a or missing	35	11
Status at last time of follow-up (343)		
alive	196	57
death	138	40
lost to follow-up	9	3
Cause of death (138)		
DLBCL	79	58
treatment DLBCL	15	11
other	32	23
unknown	12	8

Abbreviations: ICT: immunochemotherapy; CR(u): complete remission (unconfirmed); PR: partial remission; SD: stable disease; PD: progressive disease; n/a: not applicable; IQR: interquartile range.

4. Discussion

In this observational, population-based cohort study in patients with DLBCL, where two third was positioned in a low neighborhood SES, no inequalities were observed in the initiation of standard immunochemotherapy and the ability to complete treatment between patients with low, intermediate or high SES. In addition, SES was no statistically significant predictor of overall survival in this patient cohort. To our knowledge this is the first detailed documentation of treatment across different SES groups with information in the use of standard treatment protocols in patients with DLBCL.

Previous reports from the USA reported a strong association between low SES and inferior outcome in patients with NHL and particularly with DLBCL [7,12,24]. In elderly patients with NHL low neighborhood, SES was associated with increased mortality risk, and differences between ethnic groups were diminished after correction for neighborhood SES [24]. Low neighborhood SES had a substantially worse outcome after being diagnosed with DLBCL, with persistent survival disparities after the introduction of rituximab. These inequalities were at least partially explained by inadequate insurance coverage as this might contribute to limited or delayed access to health care and suboptimal treatment [7].

Table 3
Predictors for initiation and completion of standard immunochemotherapy (ICT) in patients with DLBCL by use of logistic regression models.

	Standard ICT initiated N = 293		Standard ICT completed N = 249	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
SES				
low	1	1	1	1
intermediate	0.95 (0.39–2.30)	0.99 (0.29–3.38)	0.60 (0.25–1.45)	0.51 (0.19–1.37)
high	1.02 (0.43–2.47)	2.08 (0.53–8.42)	0.55 (0.23–1.34)	0.64 (0.21–1.94)
Age				
<60	**1**	**1**	**1**	**1**
60–79	**0.36 (0.10–1.26)**	**0.35 (0.07–1.75)**	**0.12 (0.03–0.52)**	**0.15 (0.03–0.69)**
≥80	**0.04 (0.01–0.15)**	**0.07 (0.01–0.35)**	**0.03 (0.007–0.16)**	**0.05 (0.01–0.23)**
Gender				
male	1		1	
female	0.72 (0.39–1.31)		0.77 (0.40–1.47)	
Performance status				
0–1	1	1	1	1
≥2	**0.05 (0.02–0.11)**	**0.05 (0.02–0.13)**	**0.24 (0.11–0.52)**	**0.20 (0.08–0.52)**
CCI				
0–1	1	1	1	1
≥2	**0.39 (0.20–0.77)**	**0.36 (0.14–0.91)**	**0.25 (0.11–0.46)**	**0.22 (0.10–0.50)**
Place of residence				
urban	1		1	
rural	1.48 (0.79–2.78)		1.40 (0.70–2.79)	

In bold statistical significant variables with *P*-value <0.05.
Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval; SES: neighborhood socioeconomic status, divided in low, intermediate and high based on the 4-digit postal code; CCI: Charlson Cormorbidity Index.

Table 4
Predictors of overall survival in patients with DLBCL with use of a Cox proportional hazard model.

	Crude analysis HR (95% CI)	Adjusted analysis HR (95% CI)
SES		
low	1	1
intermediate	1.07 (0.66–1.74)	1.31 (0.78–2.18)
high	0.95 (0.57–1.57)	0.83 (0.48–1.46)
Gender		
male	1	
female	0.96 (0.68–1.34)	
Age		
<60	1	1
60–80	**3.42 (1.93–6.07)**	**3.01 (1.65–5.48)**
>80	**8.06 (4.43–14.69)**	**4.28 (2.21–8.31)**
Ann Arbor Stage		
1	1	
2–4	2.49 (1.51–4.09)	
Extranodal disease		
0–1	1	
≥2	1.14 (0.75–1.73)	
Performance status		
0–1	1	1
≥2	**4.35 (3.04–6.24)**	**3.27 (2.19–4.89)**
LDH		
normal	1	1
elevated	**1.87 (1.32–2.64)**	**1.92 (1.32–2.78)**
CCI		
0–1	1	1
≥2	**2.58 (1.78–3.74)**	**2.47 (1.66–3.69)**
Place of residence		
urban	1	
rural	**0.69 (0.49–0.98)**	

*In bold statistical significant variables with P-value <0.05.
**Abbreviations: HR: hazard ratio; 95% CI: 95% confidence interval; LDH: lactate dehydrogenase; CCI: Charlson Comorbidity Index; SES: socioeconomic status.

In countries with a universal health care coverage system, differences in socioeconomic disparities in cancer survival in NHL patients are less clear. A recent population-based study in UK showed no socioeconomic variations across treatment, stage at presentation and survival, with use of area-based socioeconomic data [25]. However, in a large population-based study from Denmark, socioeconomic inequalities in prognostic markers and survival in patients with NHL were certainly reported [4,6]. Low SES, measured at individual level and mainly based on degree of education, was a predictor for advanced stage disease at time of diagnosis [4], and increased mortality rates after being diagnosed with NHL [6]. The presence of more advanced stage disease could only partially explain this difference. There were no treatment disparities reported in patients with low, intermediate or high SES [6] that contributed to survival disparities. However, information about treatment was missing in up to 29% of the Danish patients and detailed information about the exact chemotherapeutic regimes and treatment follow-up were not present. An explanation for the fact that we did not find a worse survival in patients with a low SES might be the different definition of SES. While the Danish study measured SES at an individual educational level, we measured SES at a neighborhood level. Where a higher educational level may influence disease behavior, such as early recognition of symptoms and ability to comply with medical advice, higher neighborhood SES reflects other (social) factors, such as better social support, access to health care, and environmental differences between neighborhoods [26].

The presence of more comorbid diseases might be another explanation for the observed effect of SES on the differences in treatment and outcome. Several Dutch studies in solid malignancies were published using the same source (SCP) for neighborhood SES data, for example breast [17], prostate [18], esophageal [19], gastric [20] and colon cancer [21]. Despite equal health care access, disparities in treatment or worse survival were noticed in those with low neighborhood SES. This was at least partially comorbidity [18,21]. Another large population-based cohort study from the Netherlands, including patients with NHL, also reported that low SES is associated with more comorbidity. This could partially explain the observed relation between lower SES and worse outcome in patients with cancer [27]. However, as illustrated in our patients with DLBCL, significant comorbidity (CCI ≥ 2) was equally distributed among the different SES. Thus, although we previously showed that significant comorbidity was associated with worse OS in patients with advanced DLBCL, this risk factor did not negatively influenced outcome in patients with low SES in our analysis [8].

This population-based study had several strengths and limitations. The use of a physician initiated registry, HemoBase, enabled us to collect complete and representative data for this region, without the risk of selection bias. The prospective design of the database provided complete and precise treatment data for all patients. This study had several limitations when interpreting the results. First, the sample-size was relatively small. Increasing sample size will lead to an increased probability of finding statistically significant effects. However, considering the point estimates for the hazard ratios of the predictors of OS, there appeared to be a large difference in these point estimates between SES and other variables. Thus, increasing the sample size will result in smaller confidence intervals, but with similar point estimates there will not lead to a clinical relevant effect. Second, the CCI was collected retrospectively from the patient medical records. To minimize the risk for incomplete data, the CCI of all patients were discussed with the treating clinicians. One of the limitations was the use of SES at neighborhood level instead of individual level. The majority of the patients in our cohort was positioned in a low neighborhood SES. However, this neighborhood SES may not always precisely represent the socioeconomic circumstances of an individual patient. While previous studies show that neighborhood SES corresponds well with individual SES [28], another study shows that area-level socioeconomic disparities in cancer mortality is only partially explained by individual SES [29]. To verify our findings of equal treatment and survival of patients with low SES, we performed a second analysis with neighborhood SES measured at smaller quarter level, as this gives a closer approximation of individual SES, which gave the same results. As a second limitation, it can be mentioned that neighborhood SES is a composite index and we had no access to the separate variables that were used in the factor analysis of this index. However, the use of a composite index is appropriate, as the separate variables often highly correlate [26]. Finally, since the majority of the patients in our cohort had a low SES, our results may not be representative for other regions in the Netherlands.

5. Conclusion

In this population-based cohort study in patients with DLBCL no disparities in treatment and survival were seen between patients with a low, intermediate or high SES. This contrasts with previous reports and may reflect the high-quality standard health care with equal access in this patient cohort. However, the recently established nation-wide hemato-oncology registry of the Netherlands Cancer Registry (NCR) collects detailed data on demographic, clinical and treatment characteristics of all patients with hematological malignancies in the Netherlands. Therefore,

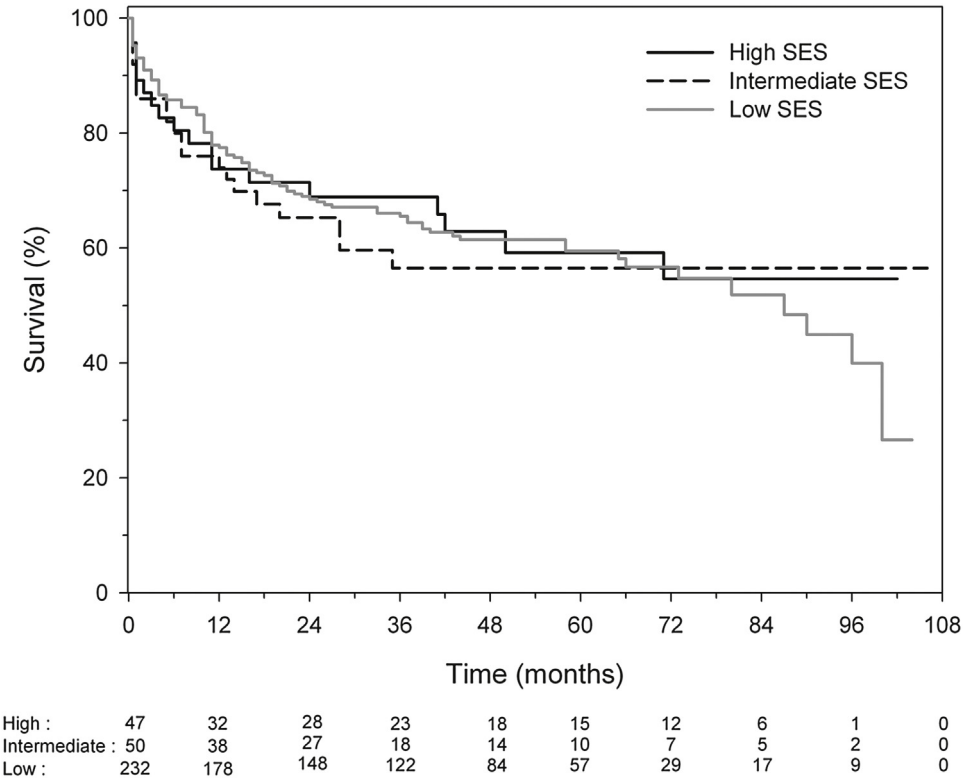

Fig. 1. overall survival in patients with low, intermediate and high SES.

we expect that data from the NCR could be used in the future to further assess disparities in care across different health care regions in the Netherlands.

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Conflicts of interest

None.

Conflict of interest statement

There is no conflict of interest by any of the authors

Authorship contribution statement

K. Boslooper collected and interpreted the data and wrote the manuscript. M. Hoogendoorn supervised the research study and is member of the project team HemoBase. E.N. van Roon and J.C. Kluin-Nelemans designed the research study. R.E. Kibbelaar reviewed the histopathological diagnosis and is member of the project team HemoBase. H. Storm designed the research study and is member of the project team HemoBase. S. Hovenga, G. Woolthuis and B.P. van Rees supervised the data collection. B. Klijs and N.J.G. M. interpreted the data and performed the statistical analysis. G.H. de Bock supervised the research study, interpreted the data and participated in writing the manuscript. All authors critically reviewed the manuscript and approved the submitted and final version.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2017.04.009.

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