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LETTER

The changing influence of neighborhood socioeconomic status on long-term survival in diffuse large B-cell lymphoma patients: A German metropolitan case-control study spanning over three decades

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An increasing body of evidence suggests that area-based socioeconomic status (SES) in addition to patient and disease characteristics might be viewed as a relevant prognostic factor for long-term survival in diffuse large B-cell lymphoma (DLBCL) patients.[1–6] Possible explanations focused on barriers to care due to lack of adequate health insurance resulting in delayed or inadequate care[1,6] while there is also evidence that large-scale implementation of CD20-directed immunochemotherapy in the standard of care considerably affected DLBCL-specific survival at the population level.[7] Here, we investigate the extent to which the introduction of rituximab-based immunochemotherapy has affected socioeconomic status (SES) disparities in all-cause overall survival (OS). This retrospective, case-control study conducts a population-based analysis in a German metropolitan area over a period of 32 years, encompassing the time before and after the introduction of up-front CD20-directed immunochemotherapy within a universal healthcare system.

DLBCL cases were reported to the Hamburg Cancer Registry between January 1, 1990 and December 31, 2022, as the first occurrence of a primary diagnosis "C83.3" according to the International Statistical Classification of Diseases, German Modification (ICD-10-GM in combination with morphology "9680" or "9684" of the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). Patients under 18 years, without a residency in Hamburg, with an incomplete record (e.g., information only from pathology report or death certificate), with a DLBCL location at the central nervous system (ICD-O-3 "C70," "C71," or "C72"), a follow-up duration of less than 3 months, or incomplete information regarding sex or SES were excluded. For assessing the impact of the introduction of modern immunochemotherapy in 2003, the sample was divided into two sub-cohorts (controls diagnosed between 1990 and 2003 and thus defining the pre-rituximab era and cases diagnosed between 2004 and 2022 defining the rituximab era). Patients with a primary diagnosis of T-cell lymphoma (ICD-10-GM coding "C84.4," "C84.6," "C84.7," "C86.5") in 1990–2022 were used as negative controls, as these patients did not benefit from the breakthrough in modern immunochemotherapy as DLBCL patient did. The SES index, hereinafter "SES," refers to the deprivation score "Sozialindex" for the City of Hamburg, which is defined for each of the 103 urban districts in Hamburg by the Social Welfare Authority of the Free and Hanseatic City of Hamburg and calculated in 2011 and 2020. The index is based on statistics related to household income, social housing, house/apartment sizes per head, and welfare reception as an indirect proxy of income.[8] Based on the quintiles of the index score the SES was grouped into low, middle, and high and thereafter assigned to patients based on their urban district of residence at the time of diagnosis. Patients were followed until death and censored in case of residence outside of Hamburg after diagnosis, after 5 years of follow-up, or at the end of the study period on December 31, 2022. Unadjusted survival differences among study groups were assessed using Kaplan–Meier functions with 95% confidence intervals and log-rank tests. Adjusted survival differences among study groups were assessed using multivariate Cox proportional hazard models, including the variables described above. To assess whether the impact of SES changed since the introduction of up-front CD20-directed immunochemotherapy (1990–2003 vs. 2004–2022), we added interactions of both variables in the model based on the epidemiological sample but also computed separate models for 1990–2003 and 2004–2022. Proportionality assumptions were assessed graphically using scaled Schoenfeld residuals. Results were expressed as hazard ratios with 95% confidence intervals. To account for correlation among patients in similar districts, cluster-robust standard errors were used. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[9] All analyses were conducted in R, Version 3.6.2. (Vienna, Austria, 2023).

In total, 2143 patients with DLBCL (median age 68, 50% males, median follow-up 3.6 years) constituted the sample covering the years 1990–2022 (Supporting Information S1: Figure S1).

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Neighborhoods with high SES were mainly concentrated in the Western and Nord-Eastern parts of Hamburg (Supporting Information S1: Figure S2). On average, patients living in neighborhoods with low SES had a lower background mortality and were treated less often at a university hospital center than those living in neighborhoods with high SES (Table 1). Comparing the period before and after the introduction of CD20-directed immunochemotherapy (R-CHOP), the share of older patients, males, and patients treated at a university hospital center increased over time.

Over the whole study period, 5-year OS improved from 53.4% to 63.5% (Figure 1). In 1990–2003, there were marked significant differences in OS between SES groups ranging from about 30% in patients living in neighborhoods with low SES to about 60% in patients living in neighborhoods with high SES (p-value 0.0011). These differentials completely diminished in the period 2004–2022, where all SES groups exhibited an almost similar survival above 60% (p-value 0.53). These findings were robust to the adjustment for the reference period, age, sex, background death probability, diagnosis at the university medical center, and prior primary tumor (Supporting Information S1: Table S1). Patients with middle SES and patients with high SES demonstrated a significantly reduced mortality risk (middle: hazard ratio: 0.54; 95% CI: 0.38–0.78, high: hazard ratio: 0.48; 95% confidence interval [CI]: 0.30–0.75) compared to the low SES group. Again, this effect was visible solely within the initial period (1990–2003), with no consistent association between SES and mortality observed in the more recent period covering the years 2004–2022 (middle SES: hazard ratio: 1.07; 95% CI: 0.71–1.43, high SES: hazard ratio: 0.92; 95% CI: 0.50–1.34). In the model testing the change in SES over time based on the full sample (1990–2022), p-values for the interaction of SES and period confirmed that indeed the relationship between both variables changed significantly. In total, 385 patients with peripheral T-cell lymphoma (median age 65, 55% males, median follow-up 3.2 years) were available for analysis (Supporting Information S1: Figure S1 and Table S2). Here, OS ranged at about 50% about the whole study period without clear differences among SES groups (Supporting Information S1: Figure S3). In the fully adjusted model, relative mortality differences between high SES and low SES were virtually similar among periods (hazard ratio for high SES in 1990–2003: 0.78; 95% CI: 0.36–1.67; 2004–2022: hazard ratio for high SES in 2004–2022: 0.81; 95% CI: 0.26–1.36; Supporting Information S1: Table S3).

Our central findings suggest that in principle advances in treatment over time benefit all societal groups, potentially

TABLE 1 Baseline characteristics of patients with diffuse large B-cell lymphoma, stratified by socioeconomic status. (A) 645 patients with diffuse large B-cell lymphoma, diagnosed in the premodern treatment era between 1990 and 2003. (B) 1498 patients with diffuse large B-cell lymphoma, diagnosed in the modern treatment era between 2004 and 2022.

(A) Pre-modern treatment era, 1990–2003		Socioeconomic status		
	Total (N = 645)	Low (N = 75)	Middle (N = 483)	High (N = 87)
Age in years, median (Q1–Q3)	66 (54, 75)	61 (50, 74)	67 (54, 75)	69 (56.50, 79)
Age ≥60 years, (%)	411 (63.7)	39 (52.0)	315 (65.2)	57 (65.5)
Background 1-year death probability, in percent, median (Q1–Q3)	1.45 (0.51, 3.41)	0.97 (0.39, 2.46)	1.46 (0.52, 3.27)	1.83 (0.55, 4.55)
Gender, male (%)	286 (44.3)	35 (46.7)	211 (43.7)	40 (46.0)
Other prior primary tumor (%)				
None	507 (78.6)	62 (82.7)	371 (76.8)	74 (85.1)
One	99 (15.3)	7 (9.3)	81 (16.8)	11 (12.6)
Two or more	39 (6.0)	6 (8.0)	31 (6.4)	2 (2.3)
Diagnosis at university hospital center (%)	109 (16.9)	8 (10.7)	80 (16.6)	21 (24.1)
Median follow-up in years (Q1–Q3)	5 (1.20, 5)	2.40 (0.85, 5)	5 (1.30, 5)	5 (1.40, 5)
Deaths within 5 years (%)	297 (46.0)	49 (65.3)	209 (43.3)	39 (44.8)
(B) Modern treatment era, 2004–2022		**Socioeconomic status**		
	Total (N = 1498)	**Low (N = 168)**	**Middle (N = 1096)**	**High (N = 234)**
Age in years, median (Q1–Q3)	69 (56, 78)	66 (55, 74)	69 (55, 78)	72 (62, 80)
Age ≥60 years, (%)	1046 (69.8)	107 (63.7)	753 (68.7)	186 (79.5)
Background 1-year death probability, in percent, median (Q1–Q3)	1.59 (0.47, 3.35)	1.17 (0.42, 2.63)	1.60 (0.43, 3.27)	1.95 (0.77, 4.31)
Gender, male (%)	789 (52.7)	88 (52.4)	579 (52.8)	122 (52.1)
Other prior primary tumor (%)				
None	1128 (75.3)	122 (72.6)	837 (76.4)	169 (72.2)
One	183 (12.2)	27 (16.1)	121 (11.0)	35 (15.0)
Two or more	187 (12.5)	19 (11.3)	138 (12.6)	30 (12.8)
Diagnosis at university hospital center (%)	293 (19.6)	25 (14.9)	213 (19.4)	55 (23.5)
Median follow-up in years (Q1–Q3)	3.20 (1.20, 5)	4.15 (1.30, 5)	3.10 (1.20, 5)	3.15 (1.30, 5)
Deaths within 5 years (%)	474 (31.6)	48 (28.6)	352 (32.1)	74 (31.6)

Abbreviations: Q1, first quartile, Q3, third quartile.

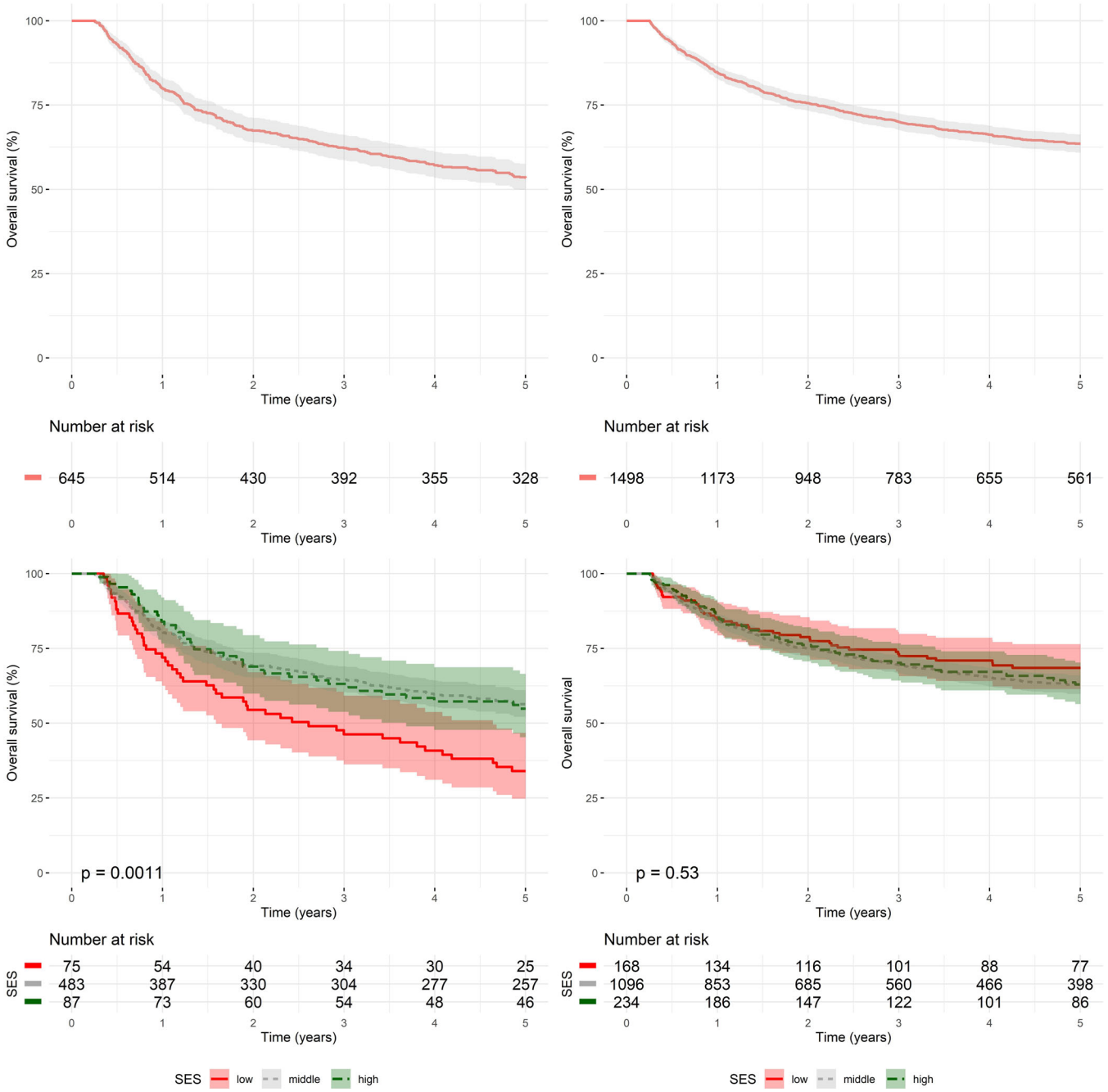

FIGURE 1 **Five-year overall survival of diffuse large B-cell lymphoma patients, stratified by socioeconomic status**. Top left and bottom (left) Hamburg premodern treatment era, 1990–2003 (*N* = 645), Top right and bottom (right) Hamburg, modern treatment era, 2004–2022 (*N* = 1498). In the years 1990–2003, 5-year overall survival was 53.4% (95% confidence interval 49.7%–57.4%) for the total cohort 34.1% (95% confidence interval 24.8%–46.8%) for patients living in low socioeconomic areas and 54.9% (95% confidence interval 45.3%–66.5%) for patients living in high socioeconomic areas. In the years, 2004–2022, 5-year overall survival was 63.5% (95% confidence interval 60.9%–66.3%), 68.5% (95% confidence interval 61.4%–76.4%), and 63.0% (95% confidence interval 56.4%–70.3%) for patients living in low and high socioeconomic areas of Hamburg, respectively.

contributing to the eradication of existing health disparities. This extends insights from a Danish population-based cohort study where educational disparities in survival after DLBCL completely diminished during the rituximab era from 2010 up until 2020.[10] In contrast, Tao et al. reported even widening survival differences among socioeconomic groups using data from 1988 to 2009.[6] Additionally, according to a recent study from Hong Kong based on 4017 DLBCL patients, low SES patients exhibited more than two times higher all-cause mortality, 53% lower odds of receiving chemotherapy, and 59% lower odds of receiving rituximab compared with patients with a higher SES.[1] Since compulsory healthcare insurance exists for all German citizens, other than in Hong Kong and the United States, inadequate insurance coverage inequalities in healthcare access are less frequent, which might be one factor explaining the differences from our results. Prior studies conducted mainly in the rituximab era from the United Kingdom, the

north-west of the Netherlands, and France did not observe survival differences between patients with low, intermediate, or high SES, aligning with our results.[11–13]

There might be alternative explanations explaining the diminishing impact of SES on survival in DLBCL patients. Possible reasons for the discussed results regarding the shifting impact of SES on the survival of DLBCL patients we found in our two observation periods. Perhaps, the composition of the patient cohorts in the two observation periods could have differed in terms of diagnosis (e.g., by recommending positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography for initial disease assessment and response evaluation), the choice of treatment approaches by performing interdisciplinary tumor conferences, the improvement of supportive measures including broad-spectrum antibiotics and granulocyte colony-stimulating factor for infection prophylaxis and treatment, and unmeasured and thus unobserved demographic characteristics, or comorbidities. Additionally, socioeconomic factors, such as income, education, and occupation, can change over time within a population. To minimize the risk that such more general structural factors may explain the change in survival differentials over the study period, peripheral T-cell lymphoma patients were employed as negative controls, as these patients were diagnosed, treated, and registered during the same time, in similar centers, but did not benefit from a breakthrough in treatment options. It is, therefore, reassuring that there was neither a general survival improvement nor changes in socioeconomic differences over time in this subgroup. This epidemiological study is based on cancer registry data, containing general information on patient characteristics and tumor diagnosis but lacking more specific prognostic variables, such as Ann-Arbor stage or IPI, information on treatment as well as lifestyle and comorbidities.

In summary, our findings reveal a shift in the effect of SES on survival over time. During our observational period, the clear advantage of patients living in high SES neighborhoods disappeared. These results suggest that improvements in treatment strategies, particularly by using rituximab-based combination with chemotherapy as first-line therapies, may have reduced the impact of SES on survival outcomes for DLBCL patients. Therefore, in line with earlier work, our findings support the idea that SES disparities could be efficiently eliminated by the implementation of modern immunochemotherapy in universal healthcare settings. Further research is needed to target barriers to timely and adequate care in countries, understand better the complex relationship between SES and survival in DLBCL patients, and ensure equitable access to effective treatments across all socioeconomic groups.

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AUTHOR CONTRIBUTIONS

Susanne Ghandili was involved in literature search, figures, study design, data analysis, data interpretation, writing—original draft, and writing—review and editing, methodology, and project administration. Judith Dierlamm was involved in supervision and validation. Carsten Bokemeyer was involved in supervision and validation. Henrik Kusche was involved in figures, study design, data collection, data analysis, data interpretation, writing—original draft, and writing—review and editing, conceptualization, data curation, formal analysis, methodology, and project administration. Frederik Peters was involved in figures, study design, data collection, data analysis, data interpretation, writing—original draft, and writing—review and editing, conceptualization, data curation, formal analysis, methodology, and project administration.

CONFLICT OF INTEREST STATEMENT

Susanne Ghandili, Judith Dierlamm, Henrik Kusche, and Frederik Peters declare no conflicts of interest. Carsten Bokemeyer declared the following conflicts of interest: Speaker: AOK Germany, Bristol Myers Squibb, med update, Merck Serono, Roche Pharma, Advisory Board: AstraZeneca, Bayer Healthcare, BioNTech, Bristol Myers Squibb, Janssen, Merck Serono, Oncology Drug Consult CRO, Sanofi Aventis.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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