

Similar Survival Between Non-Western Immigrant Patients and Danish-Born Patients with Lymphoma: A Danish Population-Based Study

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Purpose: This nationwide Danish cohort study compared overall survival (OS) between non-Western immigrant patients and Danish-born patients with lymphoma in Denmark. Furthermore, differences in clinical and socioeconomic variables were compared, and mediators of OS differences were explored to explain possible outcome differences.

Patients and Methods: The study included a total of 540 non-Western patients and 16,294 Danish-born patients diagnosed with lymphoma in the period 2000–2020. Inverse probability weighting and mediation analysis using a natural effects Cox model were used to investigate the causal relationship between immigration status and OS.

Results: Indirect effects mediated through differences in performance status and income indicated a trend towards inferior OS for non-Western immigrant patients with HRs of 1.06 (0.99–1.14) and 1.06 (0.99–1.14). However, no total causal effect of immigration status on OS was observed overall (HR: 0.94 [0.79–1.12]) and within subtype-specific analyses, except for classical Hodgkin lymphoma.

Conclusion: No significant differences in OS between non-Western immigrant patients and Danish-born patients were discovered.

Plain Language Summary: Non-Western immigrant lymphoma patients in Western countries may face multiple challenges, including lower socioeconomic status and insufficient language proficiency, which can make navigating the complexity of modern lymphoma treatment difficult. This study investigated whether the Danish tax-based healthcare system has overcome these challenges and delivered non-Western immigrant patients quality care on the same levels as that of the Danish-born patients.

Therefore, using available population based Danish registries, survival between these groups were compared, while adjusting for important clinical differences, and no significant effect of immigration status on survival was found even though non-Western immigrant patients generally had lower socioeconomic status.

Keywords: epidemiology, socioeconomics, causal inference, mediation analysis

Introduction

Overall survival (OS) after lymphoma has improved in recent decades because of more and better treatment options.^{1,2} Cancer diagnosis and treatment is a complex and life changing situation for patients and it is possible

that the ability to understand information and navigate the situation can influence outcomes. Even for patients with full proficiency in the dominant language and experience with the healthcare system, this can be difficult. For non-Western immigrants in Europe, this is even more complex and can potentially lead to poorer management of complications and compliance.

Ethnic minorities in the United States have inferior outcomes when it comes to hematological cancers,³ but this could be driven by unequal access to treatment due to socioeconomic disparities. For example, a study from California showed that patients with diffuse large B-cell lymphoma (DLBCL) living in low socioeconomic neighborhoods had substantially worse survival than those from high socioeconomic neighborhoods.⁴ The Danish healthcare system provides equal and free access to cancer treatments for all citizens, due to a tax-based system without out-of-pocket costs for the individual patient, except for over-the-counter drugs and dentistry. Therefore, possible associations between immigrant status and outcomes are less likely to be explained by inequalities in treatment access.

The present study compared OS between non-Western immigrant patients and Danish-born patients with lymphoma in Denmark. Furthermore, differences in clinical and socioeconomic variables were compared, and mediators of OS differences were explored.

Materials and Methods

In this Danish cohort study, patients diagnosed between 2000 and 2020 with classical Hodgkin's lymphoma (cHL), DLBCL, follicular lymphoma (FL), marginal zone lymphoma (MZL), or peripheral T-cell lymphoma (PTCL) were identified using the Danish National Lymphoma Registry (LYFO).⁵

Patients were categorized as non-Western immigrant, Danish-born, or neither ([Supplementary, Definitions](#)). Western immigrant patients and second-generation immigrant patients were excluded from the study.

OS was defined as time from diagnosis of lymphoma until death or censoring (31 December 2021 or emigration from Denmark), whichever came first. Unadjusted OS was computed using the Kaplan-Meier estimator and differences were tested using the Log rank test. Inverse probability weighted (IPW) Kaplan-Meier curves were weighted with age, sex, calendar year of diagnosis, and lymphoma subtype as potential confounders ([Figure S1](#)). The same weights were used in an IPW Cox model for all-cause mortality using Danish-born patients as the reference.

A mediation analysis was performed to identify potential mechanisms mediating the overall effect of immigrant status on survival. To estimate this, a natural effects Cox model⁶ was used considering Ann Arbor disease stage, Eastern Cooperative Oncology Group (ECOG) performance status, and income quartile as mediators, while controlling for confounders ([Supplementary, Interpretation of the Mediation Analysis; Figure S1](#)).

The prevalence of each lymphoma subtype among the immigrant patients and Danish-born patients was compared using logistic regression models adjusted for age. Differences in time from diagnosis to treatment for aggressive lymphomas between immigrant and Danish-born patients were compared using a linear model adjusted for age, lymphoma subtype, and year of diagnosis.

Information on income, education level, and employment status was obtained from Statistics Denmark ([Supplementary, Data Sources](#)). In all analyses, missing data was handled using a complete case approach. This study was registered in the North Denmark Region (registration number 2021–090).

Results

After the exclusion of 23 non-Western immigrant and 422 Danish-born patients due to missing data, a total of 540 immigrant patients and 16,294 Danish-born patients were included. Median age at diagnosis was 52 years for immigrant versus 66 years for Danish-born patients. Proportions of male patients were 58.1% for immigrant versus 53.4% for Danish-born patients ([Table 1](#)). Immigrant patients were more often unemployed (17.4% versus 2.7%), had reduced work capacity (20.4% versus 8.2%), and were more likely to belong to the lowest income quartile (63.7% versus 23.6%). Among the non-Western immigrant patients, the most frequent area of origin was the Middle East (41.9%) followed by Asia (23.3%), Eastern Europe (18.9%), Africa (9.8%), and Latin America (6.1%).

Table 1 Demographics Table

Variable	Level	Danish-Born Patients (n=16294)	Immigrant Patients (n=540)
Age (Years)	Median (IQR)	66 (55, 75)	52 (41.8, 65.0)
Sex	Male	8709 (53.4%)	314 (58.1%)
	Female	7585 (46.6%)	226 (41.9%)
Area of origin	Denmark	16,294 (100.0%)	0 (0.0%)
	Middle east	0 (0.0%)	226 (41.9%)
	Asia	0 (0.0%)	126 (23.3%)
	Eastern Europe	0 (0.0%)	102 (18.9%)
	Africa	0 (0.0%)	53 (9.8%)
	Latin America	0 (0.0%)	33 (6.1%)
Cohabitation	Yes	10,010 (64.2%)	360 (67.8%)
	No	5572 (35.8%)	171 (32.2%)
	Missing	712	9
Employment status	Employed	7648 (46.9%)	221 (40.9%)
	Pension	6869 (42.2%)	115 (21.3%)
	Reduced work capacity	1338 (8.2%)	110 (20.4%)
	Unemployed	439 (2.7%)	94 (17.4%)
Income quartile	Lowest	3841 (23.6%)	344 (63.7%)
	Second lowest	4216 (25.9%)	112 (20.7%)
	Second highest	4123 (25.3%)	44 (8.1%)
	Highest	4114 (25.2%)	40 (7.4%)
Educational level	Lower	12,229 (77.7%)	365 (76.2%)
	Higher	3511 (22.3%)	114 (23.8%)
	Missing	554	61
Year of Diagnosis	2000–2005	3702 (22.7%)	93 (17.2%)
	2006–2010	3684 (22.6%)	97 (18.0%)
	2011–2015	4415 (27.1%)	155 (28.7%)
	2016–2020	4493 (27.6%)	195 (36.1%)
Subtype	cHL	2130 (13.1%)	92 (17.0%)
	DLBCL	7641 (46.9%)	243 (45.0%)
	FL	3798 (23.3%)	97 (18.0%)
	MZL	1628 (10.0%)	74 (13.7%)
	PTCL	1097 (6.7%)	34 (6.3%)
ECOG	0	9280 (57.0%)	330 (61.1%)

(Continued)

Table 1 (Continued).

Variable	Level	Danish-Born Patients (n=16294)	Immigrant Patients (n=540)
	1	4412 (27.1%)	135 (25.0%)
	2	1323 (8.1%)	34 (6.3%)
	3	812 (5.0%)	29 (5.4%)
	4	467 (2.9%)	12 (2.2%)
Disease stage	1	3748 (23.0%)	134 (24.8%)
	2	2692 (16.5%)	101 (18.7%)
	3	3252 (20.0%)	111 (20.6%)
	4	6602 (40.5%)	194 (35.9%)
Follow-up (Years)	Median (IQR)	10.1 (5.6, 15.5)	8.5 (4.5, 13.5)

Notes: Demographics table showing clinical and socioeconomic factors for immigrant patients and Danish-born patients with diffuse large B-cell lymphoma.

Abbreviations: IQR, Inter quartile range; cHL, classical Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; PTCL, peripheral T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group performance status; disease stage, Ann Arbor disease stage.

Clinical Presentation

Overall, there were differences in lymphoma subtype distribution between the two groups. Non-Western immigrant patients had a higher unadjusted prevalence of cHL (17.0% versus 13.1%, [Table 1](#)) and a reduced unadjusted prevalence of FL (18.0% versus 23.3%) compared to Danish-born patients. When adjusting for age and sex, an odds ratio of 0.95 (0.92–97) for non-Western immigrant patients to have cHL compared to Danish-born patients. A similar odds ratio of 0.95 (0.92–0.99) were found when considering FL.

Time from diagnosis to treatment for aggressive lymphomas was longer for immigrant patients versus Danish-born patients (median 20 days [interquartile range [IQR]; 12–28] vs 17 days [IQR; 10–27]). Adjusted for age, lymphoma subtype, and year of diagnosis in a linear model, a difference of 1.9 days (0.6–3.2) in expected time from diagnosis to treatment between non-Western immigrant patients and Danish-born patients was found.

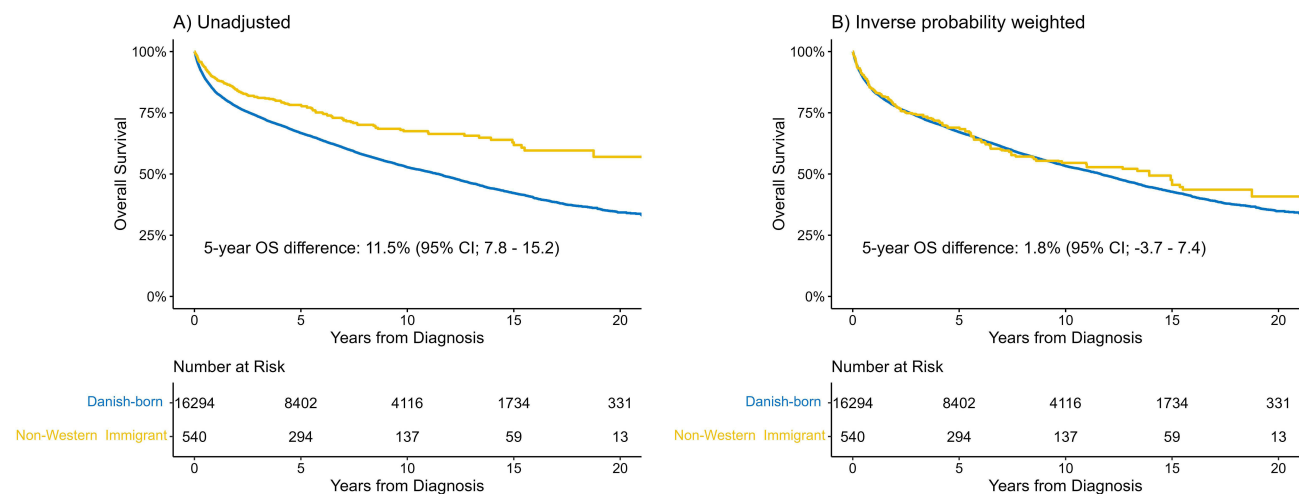


Figure 1 Overall survival for non-Western immigrant and Danish-born patients.

Notes: Unadjusted (A) and Inverse probability weighted (B) Kaplan-Meier curves and number at risk table for overall survival for immigrant patients and Danish-born patients with lymphoma.

Overall Survival

Unadjusted 5-year OS was 78.2% (95% confidence interval: 74.7–81.9) for immigrant patients versus 66.7% (66.0–67.5) for Danish-born patients, yielding a 5-year OS difference of 11.5% (7.8–15.2) (Figure 1). OS curves for the two groups became similar when using confounder-controlled IPW OS estimates, with a 5-year OS difference of 1.8(–3.7–7.4) and a corresponding IPW hazard ratio (HR) of 0.94 (0.79–1.12). Analyses of individual lymphoma subtypes were consistent with the main analysis (Figure S2), except for cHL, where an IPW HR of 0.53 (0.28–0.99) was found.

Mediation Analysis

There was no impact on survival mediated through differences in disease stages between patient groups (HR 1.00, 0.93–1.07). However, the indirect effects mediated through differences in ECOG and income quartile indicated a trend towards inferior OS for non-Western immigrant patients compared to Danish-born patients with HRs of 1.06 (0.99–1.14) and 1.06 (0.99–1.14), respectively. The direct effect of immigration status, which was not mediated through any of the considered mediators, was 0.84 (0.77–0.91). Similar results were observed when performing the same mediation analysis on a subpopulation of patients diagnosed with DLBCL (Table S1). Due to limited number of patients, this mediation analysis was not performed in other lymphoma subtypes.

Discussion

The present study did not find a worse OS for non-Western immigrant patients compared to Danish-born patients with lymphoma even after adjusting for confounders. Using mediation analysis, a direct positive effect of being an immigrant was identified, which could not be explained by mediators considered in the model. However, this positive effect was counterbalanced by the negative indirect effects of disparities in social status (income) and ECOG, thereby resulting in no overall causal effect of immigration status on OS.

These present results are in line with a Norwegian study that found similar or better OS for non-Western immigrants with solid cancer as compared to outcomes observed in the Norwegian host population.⁷ A Danish study also observed a lower all-cause mortality rate in immigrant populations compared to native Danes.⁸ Furthermore, a Dutch study found similar all-cancer survival of the Moluccans immigrants compared to the general Dutch population.⁹

The subgroup analysis for patients with cHL showed a survival advantage for immigrant patients, although the analysis was explorative in nature without correction for multiple testing. An Israeli study showed differences in gene mutation patterns between HL patients from the Eastern Mediterranean and Europe, suggesting a relevant geographical difference in HL biology, but whether this has any impact on treatment response remains unknown.¹⁰

A lower prevalence of FL was observed among the non-Western immigrant patients, in line with previous studies showing a lower age-adjusted incidence rate in Eastern Europe and Asia compared to Western Europe,¹¹ and a higher age-adjusted incidence rate of FL among non-Hispanic Whites compared to other ethnic and racial groups in the United States.¹² Some studies suggest that the incidence patterns in Asian immigrant populations become closer to the pattern observed in White populations as a Western lifestyle is adopted.¹³

A Norwegian study found that non-Western immigrants with lung and breast cancer, but not colorectal cancer, had increased time to treatment compared to Norwegians with a time to treatment HR of 0.84 (0.75–0.95).¹⁴ In the present study, immigrant patients with lymphoma had three days longer median diagnosis to treatment time for aggressive lymphomas (watch and wait not included). While the delay was statistically significant, the difference was numerically small and unlikely to impact the prognosis. The study cannot provide reasons for diagnostic delays among immigrants, but a longer time from symptom onset until diagnosis of lymphoma is not unexpected when language skills and understanding of the healthcare system are essential for clear communication of symptoms and diagnostic work-up. In the extreme, such diagnostic delays should manifest itself as later stage disease at diagnosis, but immigrant patients had a lower proportion of advanced stage disease at diagnosis (55.5% vs 60.5%) compared to the Danish-born patients. Furthermore, in the mediation analysis, there was no indirect effect on OS from disease stage, suggesting that diagnostic delays did not impact OS through more advanced stage at diagnosis among immigrants when controlling for confounders. Finally, immigrant patients were more likely to be in the lowest income quartile, which mediated a negative indirect effect of immigrant status on OS. This is also supported by previous Danish studies demonstrating that lower socio-economic groups had inferior outcomes despite healthcare being almost exclusively tax-based.¹⁵

In conclusion, despite the negative impact of lower income and worse ECOG performance status among non-Western immigrant patients, OS is equivalent to that of Danish-born patients with lymphoma. This indicates that a non-Western immigrant status does not influence outcomes of lymphoma in a tax-based healthcare system.

Data Sharing Statement

The data used in this study originates from several Danish national registries referenced in the paper and the [supplementary](#). As these registries contain personal/private information they are not publicly available and can only be accessed by applying for the data at the relevant governmental bodies responsible for the registries.

Ethics Statement

The study was registered in the North Denmark Region where the study was designed and conducted (ID: 2021-090). Danish laws state that no ethical approval or written consent are needed for retrospective studies based on register data. Data was pseudonymized and analyzed on a closed server hosted by Statistics Denmark.

Funding

This research was supported by Gilead Sciences Denmark. TCEG received funding from the Danish Cancer Society (Grant ID: R274-A17146). MRS was supported by Danish Data Science Academy (Grant ID: 2023-1210), which is funded by the Novo Nordisk Foundation (NNF21SA0069429) and VILLUM FONDEN (40516).

Disclosure

CUN received funding and/or consultancy fees from AbbVie, Janssen, AstraZeneca, Octapharma, CSL Behring, Galapagos, Takeda, Lilly, MSD, Genmab, Beigene, Danish Cancer Society, Novo Nordisk Foundation, EU ERA-PERMED, and the Alfred Benzon Foundation; advisory board member for Synamics biothec company with options for later stocks; advisory board member for DDSA, Blood, ASH. MJM has done consultancy work for Caribou, Roche, AbbVie, SOBI, Incyte, Gilead Novartis, BMS/Celgene, and Orion. LHJ is currently employed at Novo Nordisk. The remaining authors report no conflicts of interest in this work.

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