

















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Socioeconomic Status and Access to Treatment in Diffuse Large B-Cell Lymphoma

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ABSTRACT

Background and Purpose: Large B-cell lymphoma (LBCL) is the most common lymphoma subtype, with diffuse LBCL (DLBCL) accounting for 30%–40% of new lymphoma cases. The International Prognostic Index (IPI) is widely used for prognostic assessment in DLBCL. Clinical features associated with a poorer prognosis, such as advanced disease stage, could be a consequence of delayed diagnosis, which in turn may be influenced by a patient's socioeconomic status. While healthcare in Finland aims to ensure equal access to timely and high-quality treatment for all, disparities still exist. In this study we evaluated the impact of patients' socioeconomic status on their access to diagnostic procedures.

Patient/Material and Methods: Patient data was prospectively collected from seven hospitals between October 2014 and March 2020 in Finland. A total of 160 patients provided information regarding their diagnostic pathway and socioeconomic status via questionnaire. The data was combined with clinical data from patient records.

Results: The symptoms to treatment interval (STI) varied between age groups ($p = 0.019$), marital status groups ($p = 0.023$), and healthcare providers. In addition, age, income level, and occupational status (all $p < 0.001$) influenced which healthcare provider patients used as their first place of contact.

Interpretation: In this prospective study, we analyzed the impact of patients' socioeconomic status on treatment delays within the treatment pathway. Socioeconomic status was found to have a significant effect on these delays. The delays varied not only between different socioeconomic groups but also across different healthcare providers.

Kuitunen Joonas and Marin Katja have equally contributed to this article.

Kuitunen Hanne and Kuitinen Outi shares similar contributions.

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1 | Introduction

Diffuse large B-cell lymphoma (DLBCL) is part of a heterogeneous group of aggressive mature B-cell tumors that accounts for approximately 30%–40% of new lymphoma cases [1]. With an average age of 67 years at the time of diagnosis, the prevalence of DLBCL is particularly high in aging populations typical of Western countries, such as Finland, where the annual incidence rate is expected to peak in the future [2].

DLBCL is a potentially curable disease, with 60%–70% of patients achieving long-term remission with first-line treatments. However, in 30%–40% of patients, the disease relapses [3]. The prognosis for relapsed or refractory disease remains poor, but newer treatment options, such as bispecific antibodies, antibody drug conjugates, CAR-T cell therapies, and other targeted treatments, have provided a significant breakthrough, offering effective treatment options even for these challenging cases [4, 5].

The prognosis assessment and treatment decisions for DLBCL are primarily based on the clinical and biological characteristics of the disease [6–8]. In contrast, less attention has been given to non-classical factors, such as the impact of a patient's socioeconomic status. Studies on solid, hematological, and lymphatic malignancies have demonstrated the influence of lower socioeconomic status on inferior outcomes across the entire treatment pathway, from symptoms onset to post-treatment follow-up and rehabilitation. Differences in treatment outcomes may partly be explained by challenges encountered along the care pathway, such as delayed diagnosis, variations in access to treatment and treatment intensity, as well as the burden caused by the accumulation of comorbidities [9–12].

Given the aggressive nature of DLBCL, it is plausible that timely diagnosis and prompt initiation of treatment could improve prognosis. Clinical features associated with a poorer prognosis, such as advanced disease stage, could be a consequence of delayed diagnosis, which in turn may be influenced by a patient's low socioeconomic status. However, the current evidence is limited and primarily based on retrospective studies that show inconsistent results [13–15].

In Finland, primary healthcare services are provided by four publicly funded entities: the primary healthcare services of the wellbeing counties, private healthcare companies, occupational healthcare, and student healthcare. Primary healthcare is responsible for the treatment, prevention, and follow-up of common illnesses and often serves as the first point of contact within the healthcare system. If necessary, patients are referred to specialized healthcare, which provides more detailed diagnostics and advanced treatments, such as cancer therapies [16]. The goal of Finnish health policy has been to ensure equal access to high-quality and effective healthcare services for all citizens, both in primary and specialized care [17, 18].

In this present study our aim was to evaluate the influence of socioeconomic status on potential diagnostic delays among DLBCL patients by conducting a prospective study on a Finnish patient population. Knowledge about the impact of socioeconomic status on treatment outcomes has grown in recent years, but to our knowledge, we are among the first to prospectively

study the impact of socioeconomic status on treatment delays prior to treatment in patients with DLBCL.

2 | Patients/Material and Methods

This prospective study was conducted in four university hospitals and three secondary hospitals in Finland between October 2014 and March 2020. The inclusion criteria for selected patients in the study were age over 18, pathologically confirmed DLBCL diagnosis, and patients' consent to participate in the study. Recruited patients completed a questionnaire describing their socioeconomic background, primary disease symptoms, timelines for the onset of the symptoms, and contact with different levels of healthcare unit during their diagnostic and treatment processes. The data were later combined with clinical data collected from patient records, including comprehensive diagnostic pathways in secondary healthcare as well as clinical disease presentation, treatments, and disease outcome. Informed consent and questionnaires were received from 170 patients, but 10 patients were excluded from the analysis due to central nervous system localization only or a final pathological diagnosis other than confirmed DLBCL. In total, 160 patients with a histologically confirmed DLBCL diagnosis were included in the study.

Patient-reported and archive-recorded timestamps were utilized to calculate treatment delays. Time intervals were calculated as the difference between exact dates recorded for events occurring in the treatment pathway. The time from symptoms to treatment initiation was determined by subtracting the reported date of symptoms' onset from the exact date of treatment initiation. Similarly, other intervals, such as the time from first healthcare contact to meeting a physician or referral to treatment, were calculated using the precise dates recorded for each respective event.

Categorical variables, such as patient demographics, socioeconomic variables, and healthcare providers, were summarized using frequencies and percentages. Continuous variables, such as time intervals, were reported as means, medians, mean ranks, and ranges.

Differences between categorical variables were analyzed using Chi-square tests when the expected cell count was ≥ 5 or Fisher's exact test when the expected cell count was < 5 . The Mann–Whitney U test was used for pairwise comparisons and the Kruskal–Wallis test for comparisons involving more than two groups to assess differences in continuous variables (time intervals) between socioeconomic groups.

All analyses were conducted with the IBM SPSS statistics-program (Version 29.0.2.0) and a $p \leq 0.05$ was considered statistically significant.

3 | Results

3.1 | Patient Demographics According to Place of First Contact

The characteristics of all patients divided by the initial contact place of healthcare providers are presented in Table 1.

TABLE 1 | Patient demographics.

Variable <i>n</i> (%)	All <i>n</i> = 160 (%)	Healthcare provider					
		Primary healthcare emergency services	Specialist healthcare emergency services	Primary healthcare by appointment	Occupational healthcare	Private healthcare	Other
Contact place	156 (97.5)	39	8	48	19	20	22
Missing	4 (2.5)						
Age group							
18–50years	16 (10.0)	4 (10.3)	1 (12.5)	2 (4.2)	4 (21.1)	3 (15.0)	2 (9.1)
51–70years	92 (57.5)	20 (51.3)	4 (50.0)	25 (52.1)	15 (78.9)	14 (70.0)	14 (63.6)
> 70years	52 (32.5)	15 (38.5)	3 (37.5)	21 (43.8)	0 (0.0)	3 (15.0)	6 (27.3)
Sex							
Male	90 (56.3)	17 (56.4)	4 (50.0)	31 (64.6)	13 (68.4)	14 (70.0)	10 (45.5)
Female	70 (43.8)	22 (43.6)	4 (50.0)	17 (35.4)	6 (31.6)	6 (30.0)	12 (54.5)
Income							
< 1500€	60 (37.5)	18 (46.2)	4 (50.0)	18 (37.5)	1 (5.3)	5 (25.0)	11 (50.0)
1500–2999€	65 (40.6)	17 (43.6)	3 (37.5)	23 (47.9)	8 (42.1)	8 (40.0)	5 (22.7)
3000–4999€	20 (12.5)	3 (7.7)	1 (12.5)	4 (8.3)	4 (21.1)	3 (15.0)	5 (22.7)
> 5000€	9 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	6 (31.6)	3 (15.0)	0 (0.0)
Missing	6 (3.8)	1 (2.6)	0 (0.0)	3 (6.3)	0 (0.0)	1 (5.0)	1 (4.5)
Marital status							
Unmarried	18 (11.3)	4 (10.3)	1 (12.5)	8 (16.7)	1 (5.3)	2 (10.0)	2 (9.1)
Married	108 (67.5)	24 (61.5)	3 (50.0)	31 (64.6)	16 (84.2)	16 (80.0)	14 (63.6)
Divorced	12 (7.5)	3 (7.7)	2 (25.0)	3 (6.3)	1 (5.3)	0 (0.0)	2 (9.1)
Widow	19 (11.9)	7 (17.9)	1 (12.5)	5 (10.4)	1 (5.3)	1 (5.0)	4 (18.2)
Not classified	2 (1.3)	1 (2.6)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Occupation							
Management	10 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	8 (42.1)	1 (5.0)	1 (4.5)
Employee	46 (28.7)	9 (23.1)	3 (37.5)	15 (31.3)	8 (42.1)	4 (20.0)	6 (27.3)
Entrepreneur	16 (10.0)	4 (10.3)	2 (25.0)	3 (6.3)	2 (10.5)	5 (25.0)	0 (0.0)
Student	2 (1.3)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Retired	78 (48.8)	23 (59.0)	3 (37.5)	27 (56.3)	0 (0.0)	9 (45.0)	13 (59.1)
Unemployed	7 (4.4)	2 (5.1)	0 (0.0)	3 (6.3)	1 (5.3)	0 (0.0)	1 (4.5)
Missing	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Size of community							
2000–4999	23 (14.4)	4 (10.3)	0 (0.0)	9 (18.8)	0 (0.0)	1 (5.0)	8 (36.4)
5000–19,999	49 (30.6)	18 (46.2)	3 (37.5)	11 (22.9)	6 (31.6)	7 (35.0)	4 (18.2)

(Continues)

TABLE 1 | (Continued)

Variable <i>n</i> (%)	All <i>n</i> = 160 (%)	Healthcare provider					
		Primary healthcare emergency services	Specialist healthcare emergency services	Primary healthcare by appointment	Occupational healthcare	Private healthcare	Other
20,000–99,999	42 (26.3)	9 (23.1)	2 (25.0)	11 (22.9)	8 (42.1)	6 (30.0)	4 (18.2)
<100,000	43 (26.9)	8 (20.5)	3 (37.5)	16 (33.3)	5 (26.3)	5 (25.0)	5 (22.7)
Missing	3 (1.9)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (5.0)	1 (4.5)
Educational level							
No education	21 (13.1)	7 (17.9)	0 (0.0)	8 (16.7)	0 (0.0)	4 (20.0)	2 (9.1)
Lower	92 (57.5)	24 (61.5)	7 (87.5)	28 (58.3)	8 (42.1)	9 (45.0)	12 (54.5)
Higer	43 (26.9)	8 (20.5)	1 (12.5)	11 (22.9)	11 (57.9)	6 (30.0)	6 (27.3)
Missing	4 (2.5)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (5.0)	2 (9.1)

The median age of patients was 66 years, with slight male predominance. The most frequent contact place was public primary healthcare by appointment where the most common age group was 51–70 years (51.3%), followed by those aged >70 years (38.5%). Patients aged 18–50 years represented the smallest proportion in all categories, except for occupational health care, where they constituted 21.1% of patients. The gender distribution difference was most pronounced in private and occupational healthcare services, where most patients were male. Patients earning over 5000€ per month represented the smallest group in the income classification, and none of them used public healthcare services. In contrast, lower-income patients (<1500€) were concentrated in public healthcare settings, particularly in primary healthcare emergency services (46.2%). Married individuals constituted the largest proportion across all healthcare providers, ranging from 50.0% in specialist healthcare emergency to 84.2% in private healthcare. Approximately half of the patients were retired. Data S1.

3.2 | Impact of Socioeconomic Factors to STI

The comparisons between the symptoms to the treatment interval (STI) and demographic and socioeconomic factors are detailed in Table 2. The median interval STI was 102 days (mean = 148, range = 13–1124).

There was a statistically significant difference in the STI between the age groups ($p = 0.019$). Further post hoc comparisons indicated that the STI interval was significantly shorter in the 18–50 years group (mean rank = 59.17) compared to the over 70 years group (mean rank = 91.75) ($p = 0.042$). Table 3.

Marital status was also associated with variation in the STI ($p = 0.016$). Widowed patients experienced the longest intervals

(mean rank = 105.44), compared to divorced (91.75), married (75.19), and single patients (59.47). Post hoc comparisons confirmed that widowed patients had significantly longer intervals than those who were married ($p = 0.044$) or unmarried ($p = 0.013$).

Figure 1 illustrates the cumulative diagnostic time from first symptoms, various diagnostic steps until treatment start according to first place of contact.

Patients who made their first contact through primary healthcare appointments had a median STI of 127 days (mean = 201), which was significantly longer compared to patients who accessed private or occupational healthcare services, where the median STI was 76 days (mean = 126) (Mann–Whitney U , $p = 0.027$).

3.3 | Socioeconomic Factors Associated With the Place of First Contact

Socioeconomic characteristics influenced whether patients sought care through private and occupational healthcare operators or primary healthcare appointments. Age distribution differed significantly between the two healthcare providers ($p < 0.001$), with patients aged 51–70 years being more likely to use private and occupational healthcare (74.4%), whereas older individuals (>70 years) mainly accessed care through primary healthcare appointments (43.8%). Income level was significantly associated with the type of healthcare contact ($p < 0.001$), with higher-income individuals (>5000 €) predominantly utilizing private and occupational healthcare (23.1%). Occupation was another significant differentiating factor between the two groups ($p < 0.001$). Retirees formed most primary care users (56.3%), while employees and entrepreneurs were more likely to

TABLE 2 | Symptoms to treatment interval (STI) by demographic and socioeconomic factors.

Variable	All patients		STI (days)				p
	n	%	Mean	Range	Median	Mean rank	
Patients included	156	100.0	148	13–1124	102		
Sex	156						0.919
Male	89	57.0	144	13–920	100	78.18	
Female	67	43.0	153	19–1124	102	78.93	
Age category	156						0.019
18–50years	15	9.6	94	23–406	53	59.17	
51–70years	90	57.7	128	13–722	98	74.21	
> 70years	51	32.7	200	15–1124	135	91.75	
Education level	152						0.244
No education	21	13.8	229	23–1124	128	91.38	
Lower	89	58.6	137	13–613	95	73.60	
Higer	42	27.6	143	27–722	96	75.21	
Marital status	153						0.016
Unmarried	17	11.1	117	19–552	52	59.47	
Married	106	69.3	128	15–722	105	75.19	
Divorced	12	7.8	133	13–379	94	75.17	
Widow	18	11.8	307	23–1124	202	105.44	
Gross income	150						0.121
< 1,500€	58	38.7	149	13–1124	99	73.13	
1500–2999€	63	42.0	144	15–613	113	83.38	
3000–4999€	20	13.3	96	23–339	55	57.15	
> 5000€	9	6.0	185	35–772	57	76.39	
Occupation	155						0.288
Unemployed	6	3.9	149	49–406	97	84.58	
Retired	77	49.7	170	15–1124	120	85.12	
Employee	44	28.4	122	22–613	92	68.42	
Management	10	6.5	131	35–722	55	58.70	
Entrepreneur	16	10.3	139	13–384	116	81.38	
Student	2	1.3	85	52–117	85	64.50	
Size of community	153						0.701
2000–4999	22	14.4	179	22–1124	106	78.86	
5000–19,999	48	31.4	131	13–613	95	74.00	
20,000–99,999	42	27.5	144	23–722	107	83.27	
> 100,000	41	26.8	133	15–570	100	73.09	
Hospital district	155						0.155
District 1	63	40.6	142	13–920	96	71.86	
District 2	40	25.8	158	19–552	132	86.41	

(Continues)

TABLE 2 | (Continued)

Variable	All patients		STI (days)				
	n	%	Mean	Range	Median	Mean rank	p
District 3	43	27.8	166	25–1124	95	83.59	
District 4	9	5.8	77	22–138	66	56.89	

Note: The total patient cohort consisted of 160 individuals, but a time interval could only be determined for 156 patients. Additionally, in some subcategories (e.g., educational level, $n = 152$), data was not available for all patients.

use private and occupational healthcare (31.6% and 18.4%, respectively). Although marital status did not show a significant association with healthcare contact type, a higher proportion of married individuals was observed in private and occupational healthcare. Higher education levels were slightly more common among private and occupational healthcare users, although the difference was not statistically significant.

4 | Discussion and Conclusion

In this prospective study we found that higher age and widowhood were associated with longer delays in the time interval from the onset of symptoms to the initiation of treatment. Patients who sought care through private healthcare or occupational health services were typically younger, had higher incomes, and were still active in working life, whereas those using public health center services were more often older and had lower income levels. Significant differences were observed between healthcare providers in the time interval from symptom onset to the start of treatment with this interval being clearly shorter for patients accessing care through private or occupational health services.

DLBCL is an aggressive lymphatic malignancy that is potentially curable with immunochemotherapy. Despite improved disease control during the rituximab era, refractory and relapsed disease remains a major issue, causing patient suffering, lost years of life and costs to the society [19–22]. In the era of new immunological treatment modalities, such as CAR-T cell therapy and bispecific antibodies, DLBCL treatment is undergoing a rapid evolution, which will probably decrease the proportion of patients dying to DLBCL. The chances of cure could be the highest among those with early-stage disease. Two previous retrospective studies by Nikonova et al. (with 278 patients) [13], Zurko et al. (with 104 patients) [14] and one prospective study by Xavier et al. (with 42 patients) [15] evaluated the impact of diagnostic delays in DLBCL outcome. Both Zurko and Xavier found an association with inferior outcome and a diagnostic delay of over 6 months; however, this was not demonstrated in the study by Nikonova et al.

Finland has mainly a tax-paid public health care system. One of the main goals of the Finnish health policy is to offer all residents access to timely and high-quality healthcare according to need, irrespective of socioeconomic position, economic resources, or region of residence. Therefore, differences in prognosis among DLBCL patients in Finland should not, in principle, result from disparities in health care access. In our neighboring country Denmark, which has a similar tax-paid healthcare system, Frederiksen et al. found that the risk of

dying after cancer diagnosis among children was lowest in families with high income and high educational level [23]. The difference was visible despite similar treatments, and the authors speculated that this might be related to a slower diagnostic process. A similar pattern has been observed across all adults' cancer types as well, suggesting that prognosis largely depends on access to healthcare, which is also in agreement with our results [24].

The multi-channel primary healthcare system in Finland has been criticized for its structural shortcomings. Significant differences exist between service providers, particularly in terms of service availability and accessibility. These disparities contribute to inequalities between population groups, particularly between those in and outside the workforce, as well as between lower- and higher-income groups. Individuals with low income who rely on public primary healthcare services often face substantial barriers to access and utilization. In contrast, higher-income individuals, typically still active in working life, have access to comprehensive occupational healthcare services and the financial means to utilize private healthcare services as well.

The Finnish healthcare system can still be considered to follow the so-called inverse law, according to which healthcare services are most readily available to those who need them the least, and least available to those with the greatest need [25]. It is widely recognized that health in general and life expectancy improve with higher socioeconomic status. This phenomenon, known as the social gradient in health, is evident, for example, in the increased incidence of comorbidities among individuals in lower socioeconomic groups [26, 27]. Smith et al. have reported that a higher number of comorbidities is associated with prolonged delays in accessing treatment [28]. This may be related to the masking hypothesis, which suggests that cancer symptoms may go unrecognized or misinterpreted as manifestations of pre-existing conditions. Unfortunately, in this study, we were unable to assess whether delays were due to difficulties in recognizing cancer-related symptoms, symptom masking caused by comorbid conditions, or challenges in contacting healthcare services. However, it is possible that the combined effect of the inverse care law and the diagnostic complexity associated with comorbidities may partially explain the differences in treatment delays observed between socioeconomic groups.

The major strength of our study was its prospective nature, which enabled a detailed description of the patients' trajectory starting from the onset of symptoms to the initiation of treatment. The study covered a wide geographical area and included a diverse range of healthcare providers, as well as patients from different socioeconomic backgrounds.

TABLE 3 | Impact of demographic and socioeconomic factors on initial healthcare contact.

Variable	Healthcare provider		<i>p</i>
	Private and Occupational Healthcare	Primary healthcare appointment	
Sex			0.819
Male	27 (69.2)	31 (64.6)	
Female	12 (30.8)	17 (35.4)	
Age category			< 0.001
18–50 years	7 (17.9)	2 (4.2)	
51–70 years	29 (74.4)	25 (52.1)	
> 70 years	3 (7.7)	21 (43.8)	
Educational level			0.133
No education	4 (10.3)	8 (17.0)	
Lower	17 (43.6)	28 (59.6)	
Higer	17 (43.6)	11 (23.4)	
Missing	1 (2.6)	0 (0.0)	
Marital status			0.371
Unmarried	3 (7.7)	8 (16.7)	
Married	32 (82.1)	31 (64.6)	
Divorced	1 (2.6)	3 (6.3)	
Widow	2 (5.1)	5 (10.4)	
Non classified	0 (0)	1 (2.1)	
Missing	1 (2.6)	0 (0.0)	
Gross income			< 0.001
< 1500€	6 (15.4)	18 (37.5)	
1500–2999€	16 (41.0)	23 (47.9)	
3000–4999€	7 (17.9)	4 (8.3)	
> 5000€	9 (23.1)	0 (0)	
Missing	1 (2.6)	3 (6.3)	
Occupation			< 0.001
Unemployed	1 (2.6)	3 (6.3)	
Retired	9 (23.1)	27 (56.3)	
Employee	12 (30.8)	15 (31.3)	
Management	9 (23.1)	0 (0.0)	
Entrepreneur	7 (17.9)	3 (6.3)	
Missing	1 (2.6)	0 (0.0)	
Size of community			0.055
2000–4999	1 (2.6)	9 (18.8)	
5000–19,999	13 (33.3)	11 (22.9)	
20,000–99,999	14 (35.9)	11 (22.9)	
> 100,0000	10 (25.6)	16 (33.3)	
Missing	1 (2.6)	1 (2.1)	

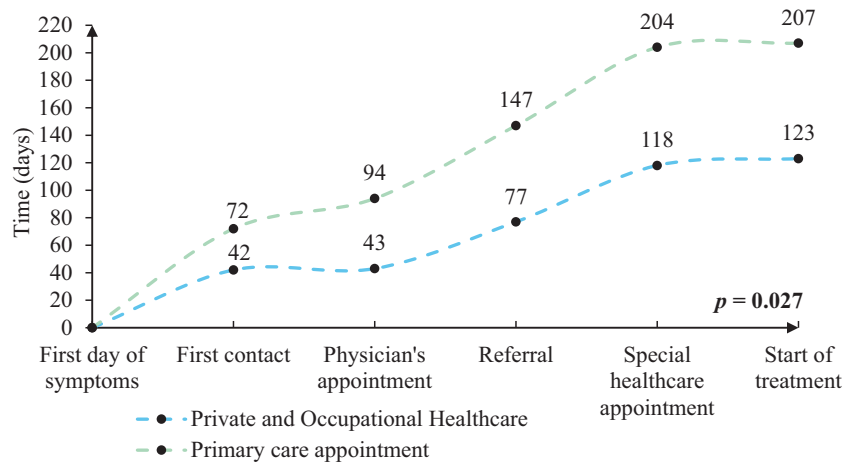


FIGURE 1 | Timeline from first symptoms to treatment: Private and occupational healthcare vs. Primary healthcare appointment pathways. The p value only describes the difference between treatment pathways from onset of symptoms to the start of treatment.

This study had some limitations. The small sample size meant that treatment delays did not follow a normal distribution when analyzed across different variables. This limited the use of statistical parametric tests. Nevertheless, appropriate non-parametric tests were used, which do not require the assumption of normality. In addition, some patient-reported variables, such as symptom onset, were derived from patient self-reports and were not consistently documented in medical records, which may introduce recall or reporting bias. It is important to confirm these findings in a larger dataset and evaluate the impact of delays and socioeconomic factors on prognosis, as well as to clarify how comorbidities contribute to these delays.

In this prospective study, we analyzed the impact of patients' socioeconomic status on treatment delays occurring within the treatment pathway. Socioeconomic status was found to have a significant effect on treatment delays. These delays not only varied between patients but also across different healthcare providers. Furthermore, socioeconomic status served as an indicator influencing the initial point of contact with healthcare services. Our findings are concerning and should be considered in political decision-making aimed at promoting equity in healthcare, and particularly in cancer care, regardless of the patient's socioeconomic status.

Author Contributions

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Ethics Statement

This study was approved by the ethics committee of the Northern Ostrobothnia Care District and was conducted according to the Good Clinical Practice guidelines of the Helsinki Declaration. All the patients joining the study provided informed consent before completing the questionnaire.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supporting Information.