Cancer Epidemiology 98 (2025) 102875

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Impact of socioeconomic individual and ecological factors on extreme diagnosis-to-treatment interval in diffuse large B-Cell lymphoma in the French real-world cohort REALYSA

Christelle Cantrelle [a], Aurélien Belot [b], Alain Monnereau [a,c], Fontanet Bijou [d], Cédric Rossi [e], Côme Bommier [f], Hadia Khebbeb Hafirassou [b], Ludovic Fouillet [g], Hervé Ghesquières [h], Loic Ysebaert [i], Sandra Le Guyader Peyrou [a,c,*]

[a] Bordeaux Population Health Research Center, EPICENE, UMR 1219, Univ. Bordeaux, Inserm, Bordeaux, France
[b] LYSARC, The Lymphoma Academic Research Organisation, Hôpital Lyon Sud, Pierre-Bénite, France
[c] Registre des hémopathies malignes de la Gironde - Institut Bergonié, Bordeaux, France
[d] Hématologie, Institut Bergonié, Comprehensive Cancer Center, Bordeaux, France
[e] CRCT, IUCT Oncopole, Dijon, France
[f] Hémato-Oncologie DMU DIH, Hôpital St Louis, InsermU1153 ECTRRA Team, 1 avenue Claude Vellefaux, Paris 75010, France
[g] Hématologie, C.H.U de Saint Étienne, Saint-Priest-en-Jarez, France
[h] Department of Hematology, Hopital Lyon Sud, Claude Bernard Lyon 1 University, Pierre Benite, France
[i] Hématologie clinique, IUCT Oncopole, Toulouse, France

ARTICLE INFO

Keywords:
Non-Hodgkin lymphoma
Diffuse large B-cell lymphoma
Old patients
Socioeconomic factors
Real-world data
Diagnosis-to-treatment interval

ABSTRACT

Introduction: Diffuse large B-cell lymphoma (DLBCL) is an aggressive though potentially curable lymphoid malignancy requiring timely treatment initiation. We investigated the impact of individual socioeconomic status and home area-level (ecological) factors on the diagnosis-to-treatment interval (DTI) in DLBCL patients, focusing on extreme delays in a French real-world cohort (REALYSA).

Methods: We analyzed patients with newly diagnosed DLBCL in the multicentric prospective cohort. DTI was defined as a duration in days between diagnosis confirmation and first-line therapy. Short and long DTIs (10th percentiles) were compared to intermediate DTI using multinomial models to identify factors associated with extreme DTIs. Socio-demographic data (including sex, education, employment, marital status, social support (SSQ6-score)…) and ecological characteristics (French deprivation index, local accessibility to general practitioners) were considered.

Results: Among 889 newly diagnosed DLBCL patients (median age 66 years, 49 % with aaIPI $\geq$1, 35 % with B-symptoms, 33 % with bulky disease), median DTI was 25 days (interquartile range: 15–39 days). The 10th- and 90th-percentile for extreme DTIs were $<$ 8 and $>$ 50 days respectively. In multivariable analysis, factors associated with short DTI included aaIPI (OR=3.03, CI95 %[1.44–6.41]), bulky disease (OR=3.06, CI95 % [1.68–5.58]), and B symptoms (OR=2.35, CI95 %[1.30–4.25]) - indicating expedited treatment for aggressive presentations. Conversely, factors associated with long DTI included older age (OR$>$80 y = 3.31, CI95 % [1.39–7.89]), being a blue-collar worker or farmer (OR=2.36, CI95 %[1.18–4.73]), or changing type of treatment facility between biopsy and initial treatment.

Conclusion: In this large real-world cohort of newly diagnosed DLBCL patients, age, occupational status, and patients' pathway were linked to very long delays to treatment. Interventions to streamline DTIs, especially for older and/or blue-collar or farmer patients, and for those changing facility of treatment, are warranted to improve quality of care.

* Corresponding author at: Bordeaux Population Health Research Center, EPICENE, UMR 1219, Univ. Bordeaux, Inserm, Bordeaux, France.
E-mail address: sandra.peyrou@u-bordeaux.fr (S. Le Guyader Peyrou).

https://doi.org/10.1016/j.canep.2025.102875
Received 22 April 2025; Received in revised form 20 June 2025; Accepted 4 July 2025
Available online 14 August 2025

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive lymphoid malignancy (LM) that represents approximately one third of non-Hodgkin's lymphoma (NHL). NHL is the seventh most common and sixth most deadly malignancy in the US [1]. In France, 5581 new patients were diagnosed with DLBCL in 2023 [2] and 5-years net survival (NS) was 58 % for patients diagnosed between 2010 and 2015 [3].

Despite the improvement of survival probabilities due to treatment innovation in many countries, persistent discrepancies have often been observed despite work to reduce them ; although reducing socioeconomic inequalities in cancer is recognized as a priority for the public health agenda, differences associated with socioeconomic levels are mostly increasing [4,5]. Thus, in the United States where these discrepancies persist, recommendations were made to understand and address social determinants [6]. Even in countries with universal health coverage such as France [7] and Slovenia [8], cancer patients with a lower socioeconomic status experience lower survival and increased mortality. Comparable studies are scarce for NHL: a population-based study from France on 1165 DLBCL patients suggests that an aggregate socio-economic index was not associated on 5 years relative survival [9]. In United Kingdom, recent studies show that the most disadvantaged patients with DLBCL had a higher excess mortality compared to least deprived [10,11].

Although DLBCL affects all ages, the median of age at diagnosis in the general population is 69 and 71 years in men and women respectively [1]. Older patients (aged over 60 years) with DLBCL have a poor prognosis compared to the younger population. Older people benefit slightly less from therapeutic progress than younger people in terms of medium- or long-term survival. These observations reflect higher excesses of mortality rates in older DLBCL patients, including in the most recent years, mostly due to higher excess risk of mortality during the first 24 months following diagnosis[12]. Moreover, older patients are often excluded from clinical trials and population-based studies so that less is known about their access to treatment. A Danish population based cohort study concluded that prolonged survival is obtainable with appropriate treatment [13]. In a recent paper, we described DLBCL patients aged 60 years and over from the REal-world dAta in LYmphoma and Survival in Adults (REALYSA) cohort regarding sociodemographic, clinical and care management by age group [14]. We observed different characteristics and behavior during first year post diagnosis for the oldest old patients' group. They also experienced the lowest overall survival (OS). However, their net survival, (which is unaffected by differences in mortality from other causes than DLBCL), was not significantly different compared to their younger counterpart group showing potentially no difference in access to care.

In the care pathway process, diagnosis-to-treatment interval (DTI) is an indicator of quality of care known to be associated with prognostic clinical factors and survival in newly diagnosed DLBCL [15,16]. Several clinical factors have been founded to be associated with short DTI but little is known about the impact of socio-economic and healthcare factors in both short and long DTI that could influence patient prognosis.

We aimed to evaluate the potential association of epidemiologic factors, especially advanced age, socio-economic and ecological factors (related to home address), with extreme DTIs (short and long) in DLBCL patients. This study was conducted using data from French patients included in a prospective real-world cohort of lymphoma patients, using an appropriate method to account for multiclass DTI and missing data.

2. Material and methods

2.1. Population

Adults with a DLBCL diagnosed between 11/2018 and 12/2021 were prospectively enrolled from the French real-world multicentric cohort REALYSA (NCT03869619). REALYSA collects demographic, clinical and epidemiological characteristics of patients newly diagnosed with one of the lymphoma subtypes including DLBCL [17]. Data were extracted on the 15th of July 2023.

The REALYSA study was approved by the ethics committee responsible for oversight of institutional research, and signed informed consent was obtained from all patients.

2.2. Outcome

The DTI was defined as the number of days between the date of biopsy reaching to diagnosis and the day of therapy initiation. DTI was categorized into extreme DTIs with short defined as <8 days and long defined as >50 days. These categories correspond to the 10th and 90th percentiles, respectively, with intermediate DTI defined as >8 days and <50.

2.3. Sociodemographic characteristics

The individual covariates were: age (18–59 y/60–79 y/$\geq$80 y), sex, education according to International Standard Classification of Education, (ISCED) [18]: primary school/secondary school (ISCED2–3) /post-secondary school (ISCED4–8), marital status (alone vs in relationship), clinical factors (Age-Adjusted International Prognostic Index (aaIPI),0–1: low risk/2–3:high risk; and Bulky disease or presence of B symptoms). Performance status (PS) was categorized as 0–1 for active patients, 2–4 refers to bed-bound patients.

Occupation was categorized according to the French occupational classification (Insee - 2003) [19] which is based on socio-professional criteria grouping broad classes of occupations (employees/executives, higher professionals/workers - farmers) compared the International Standard Classification of Occupations (ISCO) [20].

The ecological variables associated with the patient's home address were: distance to the treatment facility; French Deprivation Index (Fdep); urban/suburban/rural residence status; Local Potential Accessibility (LPA) indicator (which measures the supply of and demand for general practice services, using a high value to indicate a high level of accessibility to private general practitioners) [21]; type of treatment facility (non-teaching/teaching) and change in facility type between diagnosis and treatment.

FDep is composed of socio-economic variables (household income, high school graduates, blue-collar workers in the active population, and unemployment rate) [22]. It is calculated on the French population and was categorized using tertiles , with higher values indicating greater socio-economic disadvantage.

The short version of Sarason's Social Support Questionnaire (SSQ6 score) measures two dimensions of social support satisfaction (from 0 to 54) and availability (from 6 to 36). Each support was divided in quintiles and grouped into 3 levels (low/intermediate/high). A higher score indicates greater social support [23].

2.4. Statistical analysis

Comparisons between the three DTI groups (short, intermediate and long DTI) were performed with Pearson's Chi-squared test or Fisher's exact test as appropriate.

2.5. Missing data

We used multiple imputation (MICE) to deal with individual missing data whereas reweighting (IPW) was used to correct imbalance induced by home address non-response. See supplementary material for details.

2.6. Estimation of probabilities to have short and long DTI

A multinomial regression model supports evaluation of the association between the patient characteristics and a categorical outcome that

has more than two categories: 3 categories in our case: short, intermediate and long DTI. Intermediate DTI was considered as the reference group [24]. The final multivariable model was obtained by including all variables potentially associated with DTI (univariate analysis - p-value $\leq$0.10) selecting those with clinical relevance and at least 1 modality with p-value $\leq$ 0.05. An adjusted odds ratio $>$ 1 was interpreted as an increased probability of having short (long) DTI versus intermediate DTI for each patient's characteristic.

2.7. Survival

Overall survival (OS) was described using Kaplan Meier curves. Survival time was calculated from DLBCL date of diagnosis to the date of death, or to the date of follow-up, whichever came first. All-cause mortality was defined as death from any cause. The vital status of patients was assessed at the end of follow-up and patients still alive were censored . As OS may not be the most relevant outcome in older adults, due the increased risk of death from various causes, we also estimated net survival using the Pohar-Perme method Net survival is the survival probability unaffected by differences in mortality from other causes than DLBCL.

Curves were created to present 1-year overall and net survival with a 95 % confidence interval.

For estimation, we used the French population mortality (period: 1816–2019) available on the Human Mortality Database website, and with the transrate function implemented in the "relsurv" R package.

All tests were two-sided and p $<$ .05 was considered statistically significant.

Analyses were performed with R software version 4.2.2 (mice, nnet Packages).

2.8. Sensitivity analysis (on supplementary material)

Analyses of complete case data without imputation were also performed.

3. Results

3.1 Population A total of 1214 cohort patients with DLBCL enrolled between November 2018 and December 2021 initially were included. Two patients living in overseas territories were excluded. Of the 1212 remaining patients, 323 were excluded for lack of home address information in the database, and 1 was excluded because this patient did not receive treatment. Thus, 889 patients treated and provided home address data at diagnosis were included (Fig. 1).

3.1. Population

Among the remaining 889 patients, the median age at diagnosis was 66 years (IQR, 53–73 years) and 56 % were men. Half of the patients (49 %) had aaIPI greater than 1; one third of the patients presented B symptoms (35 %) or Bulky disease (33 %). Almost half of the patients have no comorbidity (Table 1).

Sixty-six percent of the patients lived as a member of a couple, most of them in urban zone (69 %) or in least disadvantaged areas (82 %). The median transportation time to a home care facility duration was 29 min.

Regarding the care pathway, most of patients reported being cared for in teaching hospitals (87 %). For these patients, diagnosis and treatment mainly took place in the same type of facility, accounting for 58 % of patients.

Farmers (n = 22) and blue-collar workers (n = 154) were grouped

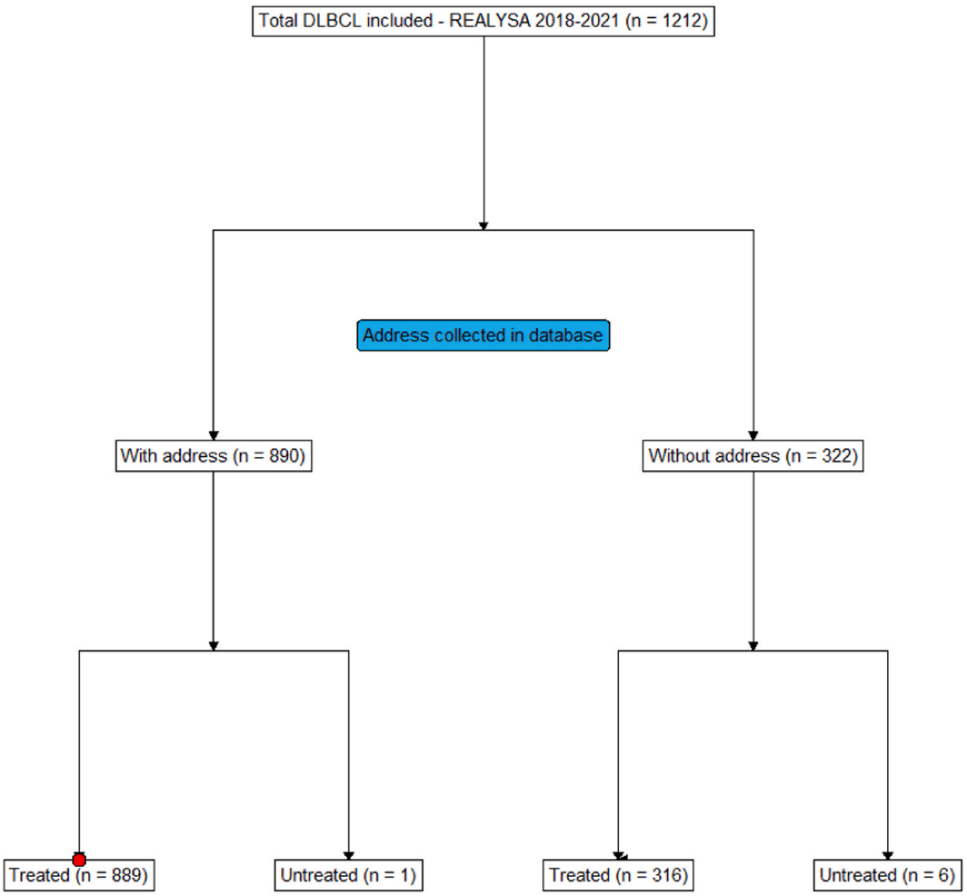

Fig. 1. Flow chart – adults included in the REALYSA cohort between November 2018 and December 2021 (N = 1212).

Table 1
Univariate analysis of patient's characteristics association with short or long DTIs: (n = 889) – adults with home address available included in the REALYSA cohort between November 2018 and December 2021 (N = 889).

Characteristic		< 8 days, N = 76[a]	[8–50 days], N = 725[a]	> 50 days, N = 88[a]	p-value[2]	Overall, N = 889[a]
Sociodemographic						
Age at diagnosis (years)					0.017	
	18–59	35 (46 %)	275 (38 %)	19 (22 %)		329 (37 %)
	60–79	36 (47 %)	384 (53 %)	59 (67 %)		479 (54 %)
	80–100	5 (6.6 %)	66 (9.1 %)	10 (11 %)		81 (9.1 %)
Age at diagnosis Median (IQR)		63 (38−73)	65 (52−73)	69 (63−74)	0.004	66 (53−73)
Male		41 (54 %)	407 (56 %)	50 (57 %)	> 0.9	498 (56 %)
Marital status					0.2	
	Single, divorced, widowed	21 (28 %)	187 (26 %)	26 (30 %)		234 (26 %)
	Maried, in a relationship	48 (63 %)	486 (67 %)	50 (57 %)		584 (66 %)
	Missing	7 (9.2 %)	52 (7.2 %)	12 (14 %)		71 (8.0 %)
Education					0.006	
	Secondary school or lower	24 (32 %)	298 (41 %)	41 (47 %)		363 (41 %)
	Post-secondary	20 (26 %)	181 (25 %)	8 (9.1 %)		209 (24 %)
	Missing	32 (42 %)	246 (34 %)	39 (44 %)		317 (36 %)
Profession					0.092	
	Employees	13 (17 %)	144 (20 %)	16 (18 %)		173 (19 %)
	Chief executives, higher professions	33 (43 %)	278 (38 %)	29 (33 %)		340 (38 %)
	Blue-collar, Farmer	8 (11 %)	142 (20 %)	26 (30 %)		176 (20 %)
	Missing	22 (29 %)	161 (22 %)	17 (19 %)		200 (22 %)
Social support						
SSQ6 availability					0.045	
	[0,16[	23 (30 %)	209 (29 %)	26 (30 %)		258 (29 %)
	[16,26[	20 (26 %)	207 (29 %)	23 (26 %)		250 (28 %)
	[26,54]	22 (29 %)	167 (23 %)	11 (13 %)		200 (22 %)
	Missing	11 (14 %)	142 (20 %)	28 (32 %)		181 (20 %)
SSQ6 satisfaction					< 0.001	
	[0,31[	13 (17 %)	201 (28 %)	21 (24 %)		235 (26 %)
	[31,36[	20 (26 %)	121 (17 %)	22 (25 %)		163 (18 %)
	36	32 (42 %)	261 (36 %)	17 (19 %)		310 (35 %)
	Missing	11 (14 %)	142 (20 %)	28 (32 %)		181 (20 %)
Living area						
French deprivation index (Fdep)					0.5	
	Low deprived (Tertile 1)	15 (20 %)	132 (18 %)	12 (14 %)		159 (18 %)
	Deprived (Tertiles 2 & 3)	61 (80 %)	593 (82 %)	76 (86 %)		730 (82 %)
Local Potential Accessibility for GP (LPA)					0.9	
	low access (Tertile 1)	67 (88 %)	624 (86 %)	75 (85 %)		766 (86 %)
	Normal or high (Tertiles 2 & 3)	9 (12 %)	101 (14 %)	13 (15 %)		123 (14 %)
Urban/Rural area					0.2	
	Urban	58 (76 %)	495 (68 %)	56 (64 %)		609 (69 %)
	Rural	18 (24 %)	230 (32 %)	32 (36 %)		280 (31 %)
Home-Care facility duration (in min) Median (IQR)		24 (14−48)	29 (15−63)	37 (14−64)	0.4	29 (14−62)
Home-Care facility distance (in km) Median (IQR)		23 (9−55)	29 (11−74)	39 (11−77)	0.3	29 (10−73)
Clinical characteristics						
Age-adjusted International Prognosis Index					< 0.001	
	[0−1]	11 (14 %)	330 (46 %)	60 (68 %)		401 (45 %)
	[2−3]	58 (76 %)	363 (50 %)	18 (20 %)		439 (49 %)
	Missing	7 (9.2 %)	32 (4.4 %)	10 (11 %)		49 (5.5 %)
Bulky disease (> 7 cm)		38 (60 %)	194 (32 %)	12 (17 %)	< 0.001	244 (33 %)
	Missing	13	114	18		145
B_symptoms					< 0.001	
	yes	48 (63 %)	237 (33 %)	23 (26 %)		308 (35 %)
Health-related characteristics						
Charlson Comorbidity Index						
	0	33 (43 %)	340 (47 %)	36 (41 %)		409 (46 %)
	1	10 (13 %)	81 (11 %)	7 (8.0 %)		98 (11 %)
	≥ 2	2 (2.6 %)	22 (3.0 %)	2 (2.3 %)		26 (2.9 %)
	Missing	31 (41 %)	282 (39 %)	43 (49 %)		356 (40 %)
Care pathway						
Type of treatment facility					0.040	
	Teaching	59 (78 %)	637 (88 %)	75 (85 %)		771 (87 %)
	Non-teaching	17 (22 %)	88 (12 %)	13 (15 %)		118 (13 %)
Diagnosis and treatment in the same type of facility					< 0.001	
	Yes	57 (75 %)	421 (58 %)	38 (43 %)		516 (58 %)
	No	19 (25 %)	304 (42 %)	50 (57 %)		373 (42 %)

[a] n (%); Median (IQR) – [2] Pearson's Chi-squared test; Kruskal-Wallis rank sum test Teaching: University Hospital & Comprehensive Cancer Center – Non-teaching: General Hospital & private clinic

together, representing a comparable group to employees (20 % of patients). High level professionals were 38 %. Supplementary table S4 describes repartition of occupations according to ISCO: Of the 176 farmers and blue-collar workers, 31 (18 %) worked in agriculture, forestry or fishing. Unfortunately, occupation data was missing in 17 % of the cases.

Among the 173 employees, 36 % were administrative and support staff, 35 % were services and sales workers, and 21 % had elementary occupations.

3.2. Outcome

Fig. 2 shows a wide range of DTI (from 0 to 132 days) with a median of 25 days (IQR 15–39). Six patients with DTI ≥ 100 days were not found to be at higher risk. They usually lived far from a facility and four of them switched from one type of facility to a teaching center at the beginning of the care pathway. These 6 patients were all treated in a teaching center (data not shown).

3.3. Associations between factors of interest and outcome

Univariate associations with DTI are shown in Table 1. We did not observe any univariate association between extreme DTIs and gender, marital status, living in most deprived or rural areas, access to general practice services (LPA) or living far from facility of the treatment. Patients with high levels of social support seemed to have access to treatment more quickly (29 % short DTI vs 23 % intermediate DTI for SSQ6 availability and 42 % short DTI vs 36 % intermediate DTI for SSQ6 satisfaction).

Multivariable associations with DTI are shown in Table 2. High aaIPI and Bulky disease at diagnosis were associated to short DTI.

The estimated odds ratio of short vs. intermediate DTI increased by 3 times (OR=3.03, 95 %CI [1.44–6.41] and OR=3.06, 95 %CI[1.68–5.58] respectively) for those with high aaIPI or with a Bulky disease compared to those with lower aaIPI or no Bulky disease, holding the other variables constant (Table 2). This odd ratio doubles for those with B symptoms (OR=2.35, 95 %CI[1.30–4.25]). In addition to this expected association with short DTI, high aaIPI was also inversely associated with less long DTI (OR=0.25 95 %CI[0.14–0.43]).

Patients who experienced a change in the type of facility center between diagnosis and treatment also had a greater likelihood of a longer DTI than an intermediate DTI (OR=1.86, 95 %CI [1.14–3.05]). Patients older than 60 years were strongly and independently associated with longer DTI, with 3 times more DTI over 50 days in patients aged 80 and older (OR_{60-79y}= 2.52, 95 %CI[1.34–4.73] and OR_{80y}= 3.31, 95 %CI [1.39–7.89]). Finally, blue-collar workers and farmers represented a socio-professional category that had an independently higher risk of having a long DTI compared to employees (OR= 2.36, 95 %CI [1.18–4.73]).

Fig. 3 summarizes the key findings, showing the significant factors associated with extreme DTIs.

3.4. Sensitivity analysis

Complete-case model analysis confirmed results obtained in our final model. It should be noted that the association between occupation and long DTI (OR= 2.24, 95 %CI[0.99–5.06]) as well as that with change of center type (OR= 1.78, 95 %CI[1.00–3.18]) are at the limit of

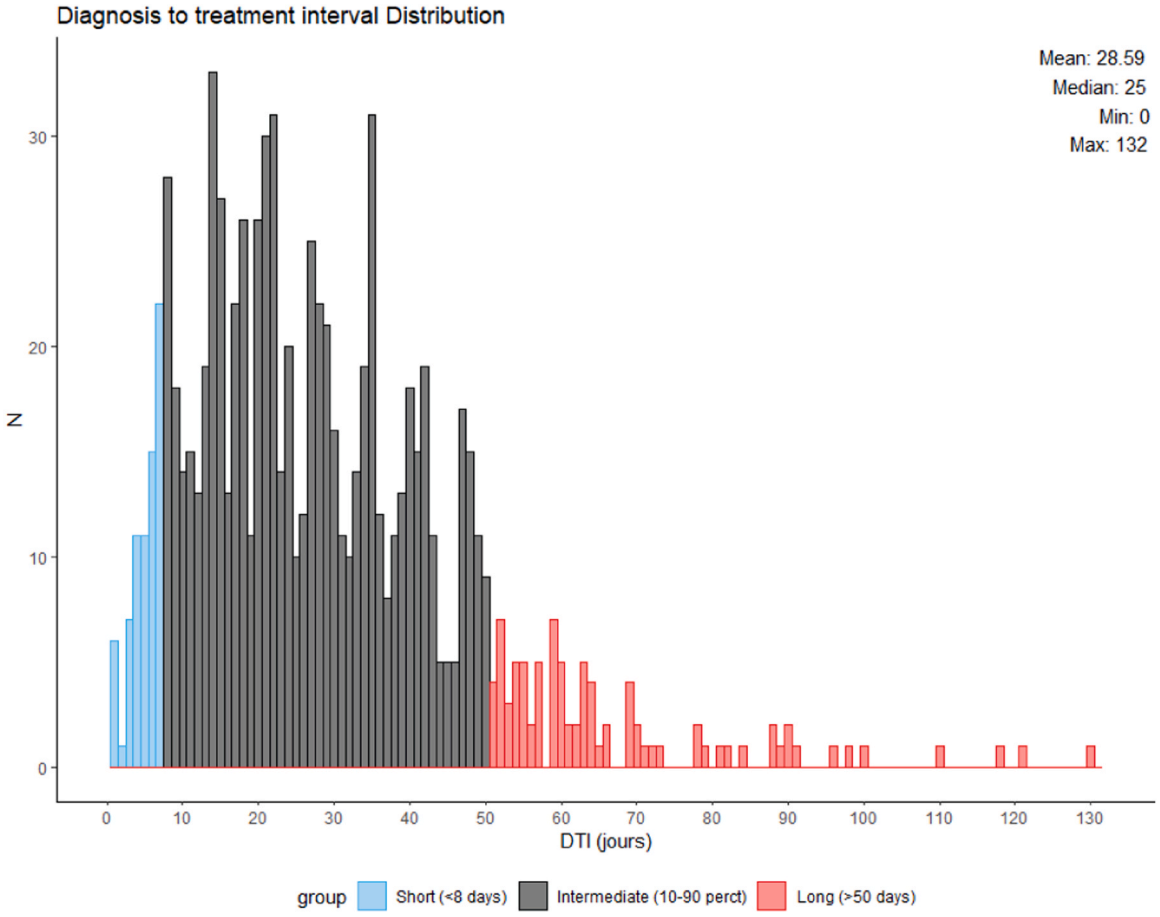

Fig. 2. DTI distribution and categorisation– adults with home address available included in the REALYSA cohort between November 2018 and December 2021 (N = 889).

Table 2
Multivariable model of short or long DTIs: the final model – adults with home address available included in the REALYSA cohort between November 2018 and December 2021 (N = 889). The multinomial logistic regression model weighted by address score (IPW) using MICE method give the Odds Ratio related to probability to have short and Long DTIs versus intermediate DTI. (Akaike information criterion (AIC) = : 809.8861).

	short DTI (<8days)			Long DTI (>50days)		
	OR[a]	95 % CI[a]	p-value	OR[a]	95 % CI[a]	p-value
Age at diagnosis (years)						
18–59	—	—		—	—	
60–79	0.69	0.37–1.28	0.2	2.52	1.34–4.73	0.004
80–100	0.55	0.17–1.80	0.3	3.31	1.39–7.89	0.007
Adjusted on age International Prognostic Index (aaIPI)						
[0−1]	—	—		—	—	
[2,3]	3.03	1.44–6.41	0.004	0.25	0.14–0.43	< 0.001
Bulky disease (> 7 cm)						
No	—	—		—	—	
Yes	3.06	1.68–5.58	< 0.001	0.72	0.39–1.31	0.3
Presence of B symptoms						
No	—	—		—	—	
Yes	2.35	1.30–4.25	0.005	0.93	0.53–1.64	0.8
Profession						
Employees	—	—		—	—	
Chief executives, higher professions	1.12	0.56–2.22	0.8	1.66	0.86–3.22	0.13
Blue-collar workers - farmers	0.43	0.16–1.18	0.10	2.36	1.18–4.73	0.016
Diagnosis and treatment in the same type of facility						
Yes	—	—		—	—	
No	0.64	0.33–1.22	0.2	1.86	1.14–3.05	0.014

[a] OR = Odds Ratio, CI = Confidence Interval

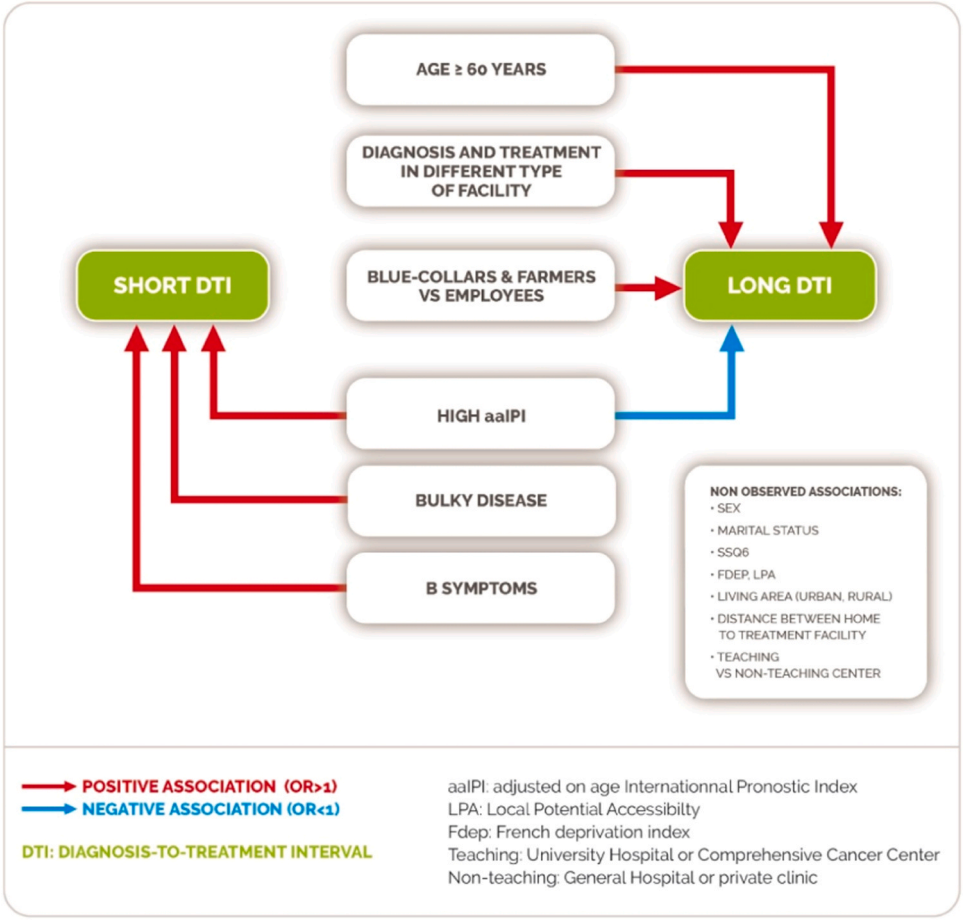

Fig. 3. Synthesis of key findings: significant factors associated with extreme DTIs.

significance (Supplementary tableS5).

3.5. Survival

When considering net survival, which represents the survival that would be observed if DLBCL was the only cause of death, we observed

significant differences between DTI groups. A short DTI was significantly associated with worse survival (Fig. 4). This result will be discussed below.

4. Discussion

DTI is influenced by both patient/system related factors and the biology of the disease. It can be misleading because short DTI often corresponds with more aggressive disease. Few studies have looked at how non-clinical factors affect DTI, except for high tumor burden measured by modern tools such as PET scans (total metabolic tumor volume) and blood ctDNA, which are strongly associated with survival in DLBCL patients [25,16] [26].

In this study, we examined how socioeconomic and ecological factors relate to the timeliness of treatment initiation in DLBCL, using real-world data from a French cohort. Our key finding is that socioeconomic disparities, even in a universal healthcare context, were associated with differences in the diagnosis-to-treatment interval. Specifically, elderly patients and blue-collar workers/farmers experienced significantly higher risks of extreme delays (>50 days) in starting therapy. Additionally, system-related factors – particularly an initial diagnosis made outside of specialized centers – contributed to delays. This is concerning from a care quality point of view and suggests room for improvement in the care pathway for various patient groups.

This work complements previous studies by describing extreme DTIs, both short and long. The probabilities of having a short or long DTIs have moved in opposite directions. Only aaIPI showed a significant association with both extremes of DTI. As expected, patients with the poorest prognosis were also associated with short DTI (high aaIPI, a large tumor mass « Bulky » and symptoms B). Fortunately, the severity of medical status of the patients' cases guides physicians to rapid diagnosis and treatment.

In the literature, the median DTI has usually chosen and used to define short DTI. Our approach fiffers in its use of the 10th and 90th percentiles. Maurer & al have shown that patients with DLBCL in LYSA European cohort initiated therapy later (LYSA median DTI, 23 days) than the United States of America cohort (MER median DTI,15 days) [25]. In our study only one third of patients initiated therapy within 15 days. Patients with short DTI (<8 days −10th percentile) correspond to cases with clinically aggressive diseases. In the French national cancer institute report, the median time to treatment was between 22 days to 26 days for DLBCL patients according to geographic district [27]. In our population, the median of age was 66 years (IQR=53–73). As patients with home address available were younger than those without address data, we estimated a median age of 68 years (IQR=56–76) in pseudo population applying weights used in multivariable model. It is consistent with several studies in DLBCL [16].

Several studies have documented the relationship between socioeconomic status (SES), healthcare utilization, and health outcomes among older adults across the globe [28]. Older patients appear to pay the price of their age, regardless of their medical condition, despite recommendations encouraging healthcare professionals to treat them after geriatric assessment guided interventions to manage non-oncological problems [29]. In the real-world, geriatric assessment at baseline is difficult to obtain because geriatricians are rarely available. In our cohort, we found that of the 323 patients aged 70 and older, 183 had an impaired Geriatric-8 score (≤14), but only 15 % of them saw an onco-geriatrician at baseline (data not shown). Because the prognosis of DLBCL is relatively poor, patients do not have enough time to perform a geriatric assessment, which likely means they incur a longer time to access treatment. In addition, the presence of more frequent comorbidities might present complexity with respect to accessing to treatment. Finally, we observed older old patients who were systematically considered too frail to receive an appropriate treatment. We found that age, by itself, still represents a loss of opportunity with respect to receipt of timely treatment, at least for some.

We examined two levels of socio-economic factors: individual occupations and indicators related to the home addresses. We found that living in a rural or deprived area and a long distance between home and treatment site or access to a general practitioner were not independent factors associated with extreme DTIs. This observation is consistent with other studies in cancer literature describing socio-economic status using indicators of deprivation and its impact on treatment and patient survival. In a country with potential free access to health care such as the Netherlands, no inequalities in treatment and survival of patients with DLBCL were found in those with lower SES [30]. In this Dutch study, neighborhood SES was defined similarly to our Fdep (mean annual income per household, percentage of households with low income, percentage of households with low education, and percentage of unemployment) at the neighborhood and district level. Our Dutch colleagues adjusted for clinical status (IPI and Charlson comorbidity index factors), sex, and age. They concluded that in their cohort of patients with DLBCL, after adjustment, no disparities in treatment and survival were seen in those with lower SES or living in rural zone. In addition, a recent population-based cohort study in Denmark, investigated the temporal trend in associations of SES with survival among 3 aggressive haematological malignant neoplasms and did not find any association for multiple myeloma and DLBCL after adjustment [31]. However, and similar to our findings, a Swedish study published by Kristinsson et al. on survival in acute myeloid leukemia and multiple myeloma found that

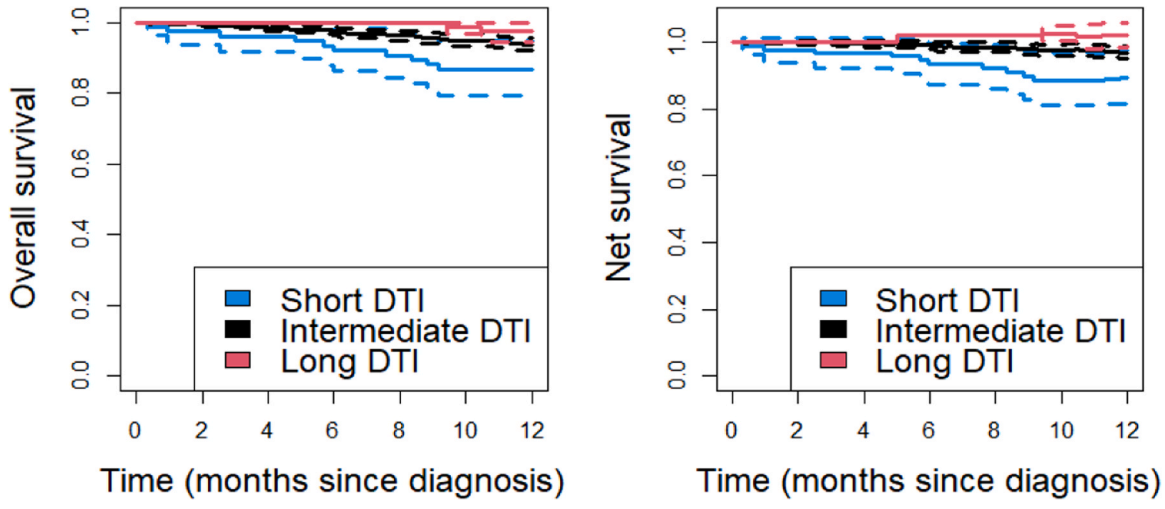

Fig. 4. Overall and net survival of REALYSA patients between November 2018 and December 2021, by type of DTI.

the differences in outcomes between white-collar workers and blue-collar workers increased over time (2000–2005: HR, 1.31, 95 %CI [1.07–1.60]). Nevertheless, in our earliest period of analysis, the difference between low and high SES groups was not statistically significant [32].

Despite the universal health coverage, and after accounting for clinical and ecological factors, the patients in our cohort who had lower individual socio-economic status incurred longer DTI. In an English study [11], 7 domains of deprivation (income, employment, education, health, crime, access to housing and services, and living environment) were considered in addition to clinical factors to estimate excess mortality. The results demonstrated the need to improve DLBCL survival in the most deprived areas of England. Similar results have been found for cancer patients in other countries. The socio-economic environment, as measured by the European Deprived Index (EDI), has been found to decrease survival probability in NHL patients in different countries [8] [11]. In the United States, DLBCL patients with lower household income, and living in non-metropolitan areas and smaller counties with limited access to health care, have considerably higher mortality risk after adjustment for various clinical predictors [33]. Despite significant progress in the fight against cancer, some populations have experienced little benefit from cancer health advances, leading to the publication of recommendations by the American Cancer Society to understand and address social determinants [6]. Our findings show that clinicians should consider age and occupation as important factors in achieving optimal care management.

The association between NHL occurrence and agricultural activities, sex, pesticide or chemical exposure has further shown that men exposed to pesticides have a higher risk of developing NHL [34]. In our study, DLBCL patients who were blue-collar workers or farmers also had a longer DTI. Indeed, of the 176 employees or farmers, 22 were farmers and 154 were employees in a farm. Furthermore, the specific occupations of the employees included various professions such as drivers, farmers, clerks, construction workers, bakers, butchers, etc. We found that the distribution by occupation was broadly similar in our study sample and in the French working population, with slightly more farmers and blue-collar workers (3.2 % in the study *versus* 1.9 % farmers in the French population and 22 % in the study versus 20 % blue-collar workers in the French population respectively) [35].

More than an occupation, this disadvantaged social category outweighs the other social aspects (living in a rural or deprived area and having a long distance between home and place of treatment or access to a general practitioner). It is well known that financial reasons are often cited as a reason for unmet health care needs. Disadvantaged social categories include patients who cannot afford to pay the advance fees, the cost of a complementary health insurance company coverage, or the other fees such as transportation associated with treatment [36]. The constraints of agricultural work, which pertain in part to people's physical abilities, can lead patients to forgo care. Their works is highly dependent on changes in the weather and requires long working hours that are difficult to combine with medical appointments [37]. To investigate this major social disadvantage, a new project (PELYCANO) in patients with DLBCL from the REALYSA cohort currently being undertaken by our team and will include an analysis of the impact of occupational pesticide exposure on response to treatment and survival.

Patient experience is poorer with delays: DLBCL patients often experience anxiety and symptomatic burden; waiting two or more months for treatment can be highly distressing and potentially allows symptoms (or the lymphoma) to worsen. However, unlike immutable risk factors, DTI can be improved with interventions. Our data identify targets for such interventions. First, streamlining referral pathways: for example, if a biopsy at a general hospital indicates DLBCL, there should be a protocol to refer that patient to a lymphoma specialist within days, not weeks. Telepathology or rapid second-opinion pathology reviews could shorten the diagnostic phase, avoiding repetitive biopsies or prolonged uncertainty. Second, patient navigation and education: in addition to education campaigns, nurse navigators could help patients schedule appointments promptly, understand the urgency of treatment, and address practical barriers (transportation, work obligations, etc.). Third, because central expertise is key for survival, centralizing complex cases through timely multidisciplinary tumor board could expedite everything.

In the present work, we reported lower 1-year OS and comparable net survival in the short compared to intermediate and long DTI for patient with DLBCL. We do not yet have the benefit of assessing survival at 5 or 10 years, wich will be interesting because clinical factors play on short DTI related to severity and therefore death. On the other hand, more socio-factors related to long DTI can also affect late results.

The strengths of this study include: first, use of a large sample of DLBCL representative of the French DLBCL population. As DLBCL usually affects adults over 60 years of age, this population is not usually involved in clinical trials. In addition, only 8 % of the patients included in our study were enrolled in a clinical trial meaning the cohort is illustrative and close to the general population's characteristics. Secondly, the study focused on socio-economic and ecological factors. REALYSA is a rich source of epidemiological data (contextual and individual information's).

A significant limitation may be the representativeness of the cohort population, and several assumptions regarding the missing data process. The high percentage of missing addresses (27 %) should be interpreted as a potential source bias. The need for caution a was foreseen in the etablishment of the cohort. Since the ecological factors were associated with home addresses we therefore used a reweighting technique to correct for nonresponse bias, of which 24 % can be explained by the composition of the REALYSA cohort.

5. Conclusions

In conclusion, independently of their own clinical risk, elderly patients with DLBCL had more extreme DTIs. Changing type of facility at the beginning of care pathway was associated to a longer access to treatment. Professional class has also played an important role: blue-collar workers and farmers had longer DTI than employees. Upon presentation of a possible diagnosis of DLBCL, clinicians should consider social determinants of health together with biological/genetic and clinical determinants, to achieve an optimal care pathway and to improve their prognostic.

CRediT authorship contribution statement

Côme Bommier: Writing – review & editing, Writing – original draft, Validation, Data curation. **Hadia Khebbeb Hafirassou:** Writing – original draft, Validation. **Ludovic Fouillet:** Validation, Data curation. **Hervé Ghesquières:** Writing – original draft, Validation, Data curation, Conceptualization. **Loic Ysebaert:** Writing – original draft, Validation, Data curation. **Sandra Le Guyader Peyrou:** Writing – review & editing, Writing – original draft, Validation, Supervision, Funding acquisition, Conceptualization. **Christelle Cantrelle:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **Aurélien Belot:** Writing – review & editing, Writing – original draft, Validation, Methodology. **Alain Monnereau:** Writing – original draft, Validation, Project administration. **Fontanet Bijou:** Validation, Data curation. **Cédric Rossi:** Validation, Data curation.

Patient consent statemennt

Written informed consent was obtained from all patients about whom research data were collected. Patients were informed of this specific analysis through a dedicated webpage on the LYSA website.

Ethics approval statement

The REALYSA study is registered at www.clinicaltrials.gov (NCT03869619) and approved by the ethics committee responsible for oversight of institutional research.

Funding

Clinical partners that provided financial support for the implementation of the REALYSA cohort included: Roche, Takeda, Janssen, Amgen, Celgene-Bristol Myers Squibb, AstraZeneca, Abbvie

This specific study was realized as post doctoral research funded by the French Cancer Research Organisation, “Sites de Recherche Intégrée sur le Cancer”(SiRIC) and "La Ligue Nationale Contre le Cancer" (Equipe de recherche labelissée).

Declaration of Competing Interest

HG has been involved in consultancy and advisory boards for Roche, Gilead, Bristol Myers Squibb(BMS) and AbbVie. CR has received a research grant from Roche and personal fees and non-financial support from Janssen, Roche, Takeda, and Abbvie. CB: JNJ (consulting), BMS (consulting), Cureety (consulting).

Acknowledgments

The authors thank the Hospices Civils de Lyon, who sponsored the study, as well as the LYSA and LYSARC, who coordinate REALYSA, in collaboration with EPICENE (Inserm) in particularly Sabine Audignon for her expertise of occupational classification. They also thank the LYSARC and EPICENE for the administration of the REALYSA database and the provision of data. The authors thank the investigating centers for their significant contributions to patient recruitment and the patients who participated to the study, whose support and collaboration made the study possible. The authors thank the French Cancer Research Agency, SIRIC (Sites de Recherche Intégrée sur le Cancer) and La Ligue Nationale Contre le cancer for funding this study. The authors also thank Robert McLaughlin for carefully (and quickly) reviewing the english language expression of this manuscript.

Finally, we are particularly grateful to Gaelle Santin, biostatistician, for her advice on handling the non-response correction, and to Béatrice Jacques and David Saint Marc for their skills in analyzing socio-economic data.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2025.102875.

References

[1] K.C. Thandra, A. Barsouk, K. Saginala, S.A. Padala, A. Barsouk, P. Rawla, Epidemiology of non-hodgkin’s Lymphoma, Med. Sci. 9 (1) (2021) 5, 30 janv.
[2] Lapôtre-Ledoux B. INCIDENCE DES PRINCIPAUX CANCERS EN FRANCE MÉTROPOLITAINE EN 2023 ET TENDANCES DEPUIS 1990 / MAIN CANCERS INCIDENCE IN METROPOLITAN FRANCE IN 2023 AND TRENDS SINCE 1990.
[3] Z. Uhry, E. Dantony, L. Roche, M. Fauvernier, C. Lecoffre, L. Lafay, et al., Survie des personnes atteintes de cancer en France métropolitaine 1989-2018 – Matériel et méthodes, Institut national du cancer, Boulogne-Billancourt, 2020.
[4] S. Vaccarella, D. Georges, F. Bray, O. Ginsburg, H. Charvat, P. Martikainen, et al., Socioeconomic inequalities in cancer mortality between and within countries in Europe: a population-based study, Lancet Reg. Health Eur. 28 (nov 2022) 100551, 25.
[5] A. Bourgeois, T.C. Horrill, A. Mollison, L.K. Lambert, K.I. Stajduhar, Barriers to cancer treatment and care for people experiencing structural vulnerability: a secondary analysis of ethnographic data, Int. J. Equity Health 30 (1) (mars 2023) 58, 22.
[6] K.I. Alcaraz, T.L. Wiedt, E.C. Daniels, K.R. Yabroff, C.E. Guerra, R.C. Wender, Understanding and addressing social determinants to advance cancer health equity in the United States: a blueprint for practice, research, and policy, CA A Cancer Journal Clinicians 70 (1) (2020) 31–46.
[7] L. Tron, M. Fauvernier, A.M. Bouvier, M. Robaszkiewicz, V. Bouvier, M. Cariou, et al., Socioeconomic environment and survival in patients with digestive cancers: a French population-based study, Cancers 13 (20) (2021) 5156.
[8] V. Zadnik, T. Žagar, S. Tomšič, A. Mihor, K. Lokar, Cancer Patients’ Survival According to Socioeconomic Environment in a High-Income Country with Universal Health Coverage, Cancers 14 (7) (2022) 1620.
[9] S. Le Guyader-Peyrou, S. Orazio, O. Dejardin, M. Maynadié, X. Troussard, A. Monnereau, Factors related to the relative survival of patients with diffuse large B-cell lymphoma in a population-based study in France: does socio-economic status have a role? Haematolgica 102 (3) (2017) 584, 92.
[10] M.J. Smith, E.N. Njagi, A. Belot, C. Leyrat, A. Bonaventure, S. Benitez Majano, et al., Association between multimorbidity and socioeconomic deprivation on short-term mortality among patients with diffuse large B-cell or follicular lymphoma in England: a nationwide cohort study, BMJ Open. Nov. 11 (11) (2021) e049087.
[11] M.J. Smith, A. Belot, M. Quartagno, M.A. Luque Fernandez, A. Bonaventure, S. Gachau, et al., Excess mortality by multimorbidity, socioeconomic, and healthcare factors, amongst patients diagnosed with diffuse large B-Cell or Follicular Lymphoma in England, Cancers 19 Nov. 13 (22) (2021) 5805.
[12] Monnereau A., Cornet E., Maynadié M., Mounier M., Troussard X., Orazio S. et al. Survie des personnes atteintes de cancer en France métropolitaine 1989-2018 – Lymphome diffus à grandes cellules B. Boulogne-Billancourt: Institut national du cancer, mars 2021, 12 p. Disponible à partir des URL: ⟨https://www.e-cancer.fr/Expertises-et-publications/Les-donnees-sur-les-cancers/Survie-des-personnes-atteintes-de-cancer-en-France-metropolitaine/e⟩.
[13] M.B. Juul, P.H. Jensen, H. Engberg, S. Wehberg, A. Dessau-Arp, D. Haziri, et al., Treatment strategies and outcomes in diffuse large B-cell lymphoma among 1011 patients aged 75 years or older: a Danish population-based cohort study, Eur. J. Cancer 99 (2018) 86–96.
[14] C. Cantrelle, A. Belot, A. Monnereau, F. Bijou, C. Rossi, H. Khebbeb Hafirassou, et al., Are oldest old patients with diffuse large B-cell lymphoma different than their younger counterparts: results from the REALYSA real-life cohort, Cancer Epidemiol. 5 (2025) 102812, 96.
[15] M.J. Maurer, H. Ghesquières, J.P. Jais, T.E. Witzig, C. Haioun, C.A. Thompson, et al., Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy, J. Clin. Oncol. 32 (10) (2014) 1066, 73.
[16] D.N. Blunt, L. Smyth, C. Nagamuthu, E. Gatov, R. Croxford, L. Mozessohn, et al., Shorter diagnosis-to-treatment interval in diffuse large B-Cell Lymphoma is associated with inferior overall survival in a large, population-based registry, J. Natl. Compr. Cancer Netw. 19 (6) (2021) 719, 25.
[17] H. Ghesquières, C. Rossi, F. Cherblanc, S.L. Guyader-Peyrou, F. Bijou, P. Sujobert, et al., A French multicentric prospective prognostic cohort with epidemiological, clinical, biological and treatment information to improve knowledge on lymphoma patients and survival in adults’, BMC Public Health 16 (2021).
[18] international-standard-classification-of-education-isced-2011-fr.pdf [Internet]. [cité 16 juin 2025]. Disponible sur: ⟨https://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-fr.pdf⟩.
[19] Institut National de la Statistique et des Etudes Economiques. PCS 2003 | Insee [Internet]. [cité 23 août 2024]. Disponible sur: ⟨https://www.insee.fr/fr/information/2400059⟩.
[20] International Labour Organization. C.I.T.P.- Classification internationale type des professions [Internet]. [cité 23 août 2024]. Disponible sur: ⟨https://webapps.ilo.org/public/french/bureau/stat/isco/⟩.
[21] Barlet M. Local Potential Accessibility (LPA): A New Measure of Accessibility to Private General Practitioners. 2012;
[22] G. Rey, E. Jougla, A. Fouillet, D. Hémon, Ecological association between a deprivation index and mortality in France over the period 1997 – 2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death, BMC Public Health (1) (2009) 33.
[23] N. Rascle, M. Bruchon-Schweitzer, I.G. Sarason, Short form of Sarason’s social support questionnaire: french adaptation and validation, Psychol. Rep. août 97 (1) (2005) 195–202.
[24] Dobson A.J. An introduction to generalized linear models. 2. ed. Boca Raton, Fla.: Chapman & Hall / CRC; 2002. 225 p. (Texts in statistical science).
[25] M.J. Maurer, H. Ghesquières, B.K. Link, J.P. Jais, T.M. Habermann, C. A. Thompson, et al., Diagnosis-to-treatment interval is an important clinical factor in newly diagnosed diffuse large B-Cell Lymphoma and has implication for bias in clinical trials, J. Clin. Oncol. 36 (16) (2018) 1603, 10.
[26] S. Alig, C.W. Macaulay, D.M. Kurtz, U. Dührsen, A. Hüttmann, C. Schmitz, et al., Short Diagnosis-to-Treatment Interval Is Associated With Higher Circulating Tumor DNA Levels in Diffuse Large B-Cell Lymphoma, J. Clin. Oncol. 39 (23) (2021) 2605, 16.
[27] Bouvier A.M., Arveux P., Baldi I., Bouvier V., Dabakuyo S., Daoulas M., et al. Quels sont les délais de prise en charge des cancers en France ? Étude menée à partir des registres de cancers [Internet]. [cité 22 août 2024]. Disponible sur: ⟨https://beh.santepubliquefrance.fr/beh/2013/43-44-45/2013_43-44-45_5.html⟩.
[28] D.J. McMaughan, O. Oloruntoba, M.L. Smith, Socioeconomic status and access to healthcare: interrelated drivers for healthy aging, Front. Public Health 18 (2020) 231.
[29] S.G. Mohile, W. Dale, M.R. Somerfield, M.A. Schonberg, C.M. Boyd, P.S. Burhenn, et al., Practical ASsessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO guideline for geriatric oncology, J. Clin. Oncol. 36 (22) (2018) 2326.

[30] K. Boslooper, M. Hoogendoorn, E.N. van Roon, R.E. Kibbelaar, H. Storm, S. Hovenga, et al., No outcome disparities in patients with diffuse large B-cell lymphoma and a low socioeconomic status, Cancer Epidemiol. 48 (2017) 110.
[31] L.H. Nielsen, D.T. Kristensen, L.H. Jakobsen, M. Bøgsted, H. Gregersen, J. Madsen, et al., Socioeconomic status and overall survival among patients with hematological malignant neoplasms, JAMA Netw. Open. 7 (3) (2024) e241112.
[32] Kristinsson S.Y., Derolf Å.R., Edgren G., Dickman P.W., Björkholm M. Socioeconomic Differences in Patient Survival Are Increasing for Acute Myeloid Leukemia and Multiple Myeloma in Sweden. Journal of Clinical Oncology [Internet]. 20 avr 2009 [cité 15 oct 2024]; Disponible sur: ⟨https://ascopubs.org/doi/10.1200/JCO.2008.18.2006⟩.
[33] S. Ketineni, C. Abro, X. Zhu, V. Prakash, S.S. Makhani, K. Robinson, et al., Impact of sociodemographic and socioeconomic factors on diffuse large b-cell lymphoma (DLBCL)-Specific mortality in the United States - a SEER PLUS database analysis spanning 20 Years, Blood 15 140 (2022) 8072.
[34] J.R. Cerhan, A. Kricker, O. Paltiel, C.R. Flowers, S.S. Wang, A. Monnereau, et al., Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-Cell Lymphoma: the InterLymph non-hodgkin Lymphoma subtypes project, JNCI Monogr. 2014 (48) (2014) 15–25.
[35] Professions et secteurs d'activité – Emploi, chômage, revenus du travail | Insee [Internet]. [cité 5 août 2024]. Disponible sur: ⟨https://www.insee.fr/fr/statistiques/6453692?sommaire=6453776⟩.
[36] Renoncement aux soins pour raisons financières | Direction de la recherche, des études, de l'évaluation et des statistiques [Internet]. [cité 11 déc 2024]. Disponible sur: ⟨https://www.drees.solidarites-sante.gouv.fr/publications/dossiers-solidarite-et-sante-1998-2016/renoncement-aux-soins-pour-raisons-financieres⟩.
[37] G. Beltran, Explications et modes de justification du renoncement aux soins dans une population ruralo-agricole. Rôles et ajustements d'un modèle de masculinité traditionnelle, Rech. Sociol. Et. Anthropol. 1 (48-1) (sept 2017) 87–107.