Cancer Epidemiology 96 (2025) 102812

Contents lists available at ScienceDirect

Cancer Epidemiology

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

Are oldest old patients with diffuse large B-cell lymphoma different than their younger counterparts: Results from the REALYSA real-life cohort

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ARTICLE INFO

Keywords:
Non-Hodgkin lymphoma
Diffuse large B-cell lymphoma
Older adults
Oldest old
Real-world data

ABSTRACT

Introduction: Over a half of diffuse large B-cell lymphoma (DLBCL) cases are diagnosed in adults aged 65 years and older. Older adults are a heterogeneous group, and few studies reported differences in care management and survival in the oldest old. We aimed to describe characteristics, care management, and survival of older adults aged 60 and over included in the REal-world dAta in LYmphoma and Survival in Adults (REALYSA) study.
Materials: and methods: Patients newly diagnosed with DLBCL, aged over 60 years, included in REALYSA cohort between 2018/11 and 2021/12 and receiving therapy (RCHOP/miniRCHOP/Other) were included. Socio-demographic, living area and clinical characteristics, as well as the type of care center and pathway during the first year after diagnosis were described by age (60–69 y/70–79 y/≥80 y). Survival was described using Kaplan-Meier curves, the Cox model for adjusted survival, and net survival (Pohar-Perme estimator).
Results: A total of 560 DLBCL patients with a median age at diagnosis of 72 years (IQR=67–77) were included. R-CHOP was the main curative treatment in patients aged 60–79, and R-miniCHOP in the oldest old. More than half of the patients were male, married or in a relationship, living in urban and low deprived area. With increasing age, the proportion of patients with performance status 0–1 or no Charlson comorbidity at diagnosis decreased. Two thirds of patients were diagnosed at advanced stage with comparable trends between age groups. However, the oldest patients were more likely to have high-risk disease and geriatric frailty at diagnosis. One-year net survival, in contrast to OS (91 %vs 95 % and 75 % for each age group), showed no significant reduction in survival for 80 + (93 %, 100 % and 87 % for each age group).
Conclusion: As the fastest-growing age group in developed countries, the oldest old require a special attention and further work on this population is needed.

1. Introduction

Non-Hodgkin lymphoma (NHL) ranks the fifth to ninth most common cancer in most developed countries [1]. Diffuse large B-cell lymphoma (DLBCL) is the most common frequent NHL subtype, accounting for approximately one third of all NHLs [2]. DLBCL often presents as an aggressive disease, becoming rapidly fatal without any treatment. Overall, the incidence of DLBCL is higher in males compared to females and increases exponentially with age [3–5]. Over a half of patients diagnosed with DLBCL are aged 65 and over, and nearly a third of DLBCL are diagnosed in adults aged 75 + [2]. As the world population is aging, the number of older patients with DLBCL will increase in the next

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https://doi.org/10.1016/j.canep.2025.102812
Received 28 June 2024; Received in revised form 21 March 2025; Accepted 28 March 2025
Available online 5 April 2025

decades [6,7].

Age over 60, included in the International Prognostic Index (IPI), is an unfavorable independent prognostic factor in DLBCL, and several studies have reported lower survival in older adults [5,8,9]. Older adults are also more likely to present poor performance status (PS) at diagnosis, the latter being highly associated with lower survival [8]. Care management in the older population may be challenging due to the presence of comorbidities, impaired functional and/or cognitive status, and a higher risk of treatment toxicities. In addition, the poor rate of inclusion of older adults in clinical trials does not facilitate treatment decision-making [10,11]. Thus, poorer outcomes among older patients with DLBCL may result from an interplay of unfavorable biology of the disease, poor health status, suboptimal management, treatment toxicities, and unmet treatment needs in this population [12].

However, older adults represent a heterogeneous group, and age cannot define by itself care management or prognosis. Several studies reported that the oldest old, defined as adults aged 80 or 85 years and older, present a lower likelihood to receive curative treatment than their younger counterparts [8]. Studies also highlighted lower survival in this population [13–15], while others reported comparable survival probabilities than younger patients only when they received treatment [5]. The oldest old are the fastest-growing age group in developed countries, and their global population worldwide is expected to triple between 2015 and 2050 [16]. Thus, the number of cancer cases and cancer deaths among this population is also projected to increase [17,18]. However, data on the oldest old population are scarce.

In the present work, we aimed to describe sociodemographic and clinical characteristics, care management and survival among adults aged 60 and over and included in the REal-world dAta in LYmphoma and Survival in Adults (REALYSA) study.

2. Materials and methods

2.1. The REALYSA study

The REALYSA study, initiated in November 2018, is a French multicentric prospective prognostic cohort set up in French areas mostly covered by population-based cancer registries [19]. This cohort aims to study the prognostic value of epidemiological, clinical and biological factors with a prospective follow-up of several years. Adult patients without lymphoma history and newly diagnosed with DLBCL, follicular, marginal zone, mantle cell, Burkitt, Hodgkin, mature T-cell lymphoma, were invited to participate during a medical consultation with their hematologist. Clinical data, epidemiological data and biological samples were collected. Among the 35 centers participating in the REALYSA cohort, 23 centers collected epidemiological data, while the others only collected clinical and treatment information. Vital status is retrieved from each follow-up at the cohort using medical records and the French national database of death. Approximatively of 6000 patients were included in the REALYSA study and the follow-up is still ongoing.

The REALYSA study was registered at www.clinicaltrials.gov (NCT03869619) and approved by ethics committee, and written informed consent was obtained from all patients. Patients were informed of this specific analysis through a dedicated webpage on the LYSA website.

2.2. Study population

Patients, included in the REALYSA study, aged 60 years and over, with a primary diagnosis of DLBCL between November 2018 and December 2021 were included in the present work. Data were extracted on July 15th 2023. As we wanted to study contextual factors that are collected in epidemiological data, we included patients from the 23 centers with epidemiological data. Due to a scarce number of patients who did not receive DLBCL-related treatment (n = 1), only treated patients were included. In addition, patients with their home address at diagnosis missing were excluded (n = 240). These individuals were described in Supplementary Material.

2.3. Study variables

Age at diagnosis was the factor of interest and was categorized in three age groups (60–69 years, 70–79 years, and 80 years and over).

In addition to age, sociodemographic factors, social support, living area-related factors, health-related factors, clinical factors, as well as geriatric assessment were considered at diagnosis.

Sociodemographic factors – Sex, marital status at diagnosis and education were considered. Marital status was grouped into 2 categories (married or in a relationship vs single, divorced, widowed) to consider the physical and emotional support what being in a couple brings [20]. Education level was group into 3 categories (Primary school or lower/ Secondary school/ Post-secondary).

Social support – The Short form of Sarason's Social Support Questionnaire (SSQ6) [21,22], a 6-item questionnaire, was used to evaluate social support. The SSQ6 distinguishes the importance of number and satisfaction of the social support, and measures two dimensions of social support, availability (from 0 to 54) and satisfaction (from 6 to 36). Each dimension divided in quantiles and grouped into low/-intermediate/high/missing levels, a higher score reports a higher social support.

Living area – Several ecological data linked to the patients' home address were considered: the French index of deprivation (Fdep), the Local Potential Accessibility to General Practitioners (LPA to GPs), the time (min) and distance (km) by car between home address and place of care. Social deprivation was measured using the Fdep, available at the municipality level [23,24]. It is the first component of a principal component analysis of four socioeconomic variables (the median household income, the percentage high school graduates in the population aged 15 years and older, the percentage blue-collar workers in the active population, and the unemployment rate). Fdep was build using data from the 2019 French national census conducted by the National Institute of Statistics and Economic Studies (INSEE). The Fdep was categorized into tertiles on French population, higher value representing a higher level of deprivation. The LPA, also available at the municipality level, measures the supply of and demand for general practice services by taking into account practitioners' volume of activity, and service use rates differentiated by population age structure [25]. The LPA to GPs showed a greater degree of variability than the traditionally used accessibility indicators (e.g. travel time). The highest tertile (calculated on French population) represents a high accessibility to GPs.

Health-related factors – The performance status (PS) was used to describe the patient's level of functioning in terms of ability to care for himself, daily activity, and physical ability at diagnosis [26]. While PS 0 means the patient is fully active, PS 4 refers to bedbound. The Charlson comorbidity Index (CCI) was collected in a specific questionnaire including epidemiological data. The CCI is a weighted (from 1 to 6) index considering 19 conditions (e.g. diabetes, dementia, ulcer disease, tumors, etc.) [27]. In the REALYSA study, patients presenting AIDS, leukemia and lymphoma comorbidities were excluded.

Clinical factors – Several clinical factors identified as relevant prognosis factors were considered. The Ann Arbor stage [28], widely used for anatomic staging of lymphoma, was determined through pathology report. The age-adjusted International Prognostic Index (aaIPI) comprises three factors (PS, lactate dehydrogenase, disseminated stage) and is used as a tool to predict survival in de novo DLBCL patients [29,30]. Bulky diseases and B symptoms were retrieved from pathology report and patient medical records.

Geriatric assessment – The Geriatric-8 (G8) screening tool [31], recommended for identifying frail patients needing specific medical care, is collected for patients older than 70 years. A score $\leq$ 14 (impaired) is indicated frailty and suggests the need for geriatric assessment.

2.4. Statistical analyses

Descriptive analyses were performed by tabulating sociodemographic, living area and clinical characteristics by age categories (60–69 y/70–79 y/≥80 y). The type of care center used along the care pathway was described using Sankey plots, stratified by age group. These plots enable visualizing the repartition and contribution to each flow of patients according to type of treatment center (university hospital, comprehensive cancer center, general hospital, private care center) through different moments of care pathway (first medical contact, diagnosis, treatment decision-making, treatment initiation).

Then, the patients' pathway during the first year from diagnosis was described by plotting the percentage of patients regarding the achievement of three different events (treatment, progression, death). The

Table 1
Characteristics of treated older adults with a diagnosis of DLBCL included in the REALYSA cohort between November 2018 and December 2021 (N = 560).

	60–69 N = 233	**70–79** N = 246	**≥ 80** N = 81	**Overall** N = 560
Sociodemographic characteristics				
Age at diagnosis Median (IQR)	66 (64–68)	74 (72–77)	84 (82–87)	72 (67–77)
Male	134 (58 %)	132 (54 %)	42 (52 %)	308 (55 %)
Marital status				
Single, divorced, widowed	56 (24 %)	73 (30 %)	30 (37 %)	159 (28 %)
Married, in a relationship	164 (70 %)	149 (60 %)	40 (49 %)	353 (63 %)
Missing	13 (6 %)	24 (10 %)	11 (14 %)	48 (9 %)
Education				
Primary school or lower	22 (9 %)	36 (15 %)	18 (22 %)	76 (14 %)
Secondary school	95 (41 %)	63 (25 %)	24 (30 %)	182 (32 %)
Post-secondary	40 (17 %)	51 (21 %)	6 (7 %)	97 (17 %)
Missing	76 (33 %)	96 (39 %)	33 (41 %)	205 (37 %)
Social support				
SSQ6 Median (IQR)	16 (11–24)	16 (11–20)	17 (12–21)	16 (11–22)
SSQ6 availability				
[0,16[	84 (36 %)	92 (38 %)	24 (30 %)	200 (36 %)
[16,26[	59 (26 %)	75 (30 %)	21 (26 %)	155 (28 %)
[26,54]	38 (16 %)	28 (11 %)	10 (12 %)	76 (13 %)
Manquant	52 (22 %)	51 (21 %)	26 (32 %)	129 (23 %)
SSQ6 satisfaction				
[0,31[	65 (28 %)	73 (29 %)	17 (21 %)	155 (27 %)
[31,36[	36 (16 %)	44 (18 %)	13 (16 %)	93 (17 %)
36	80 (34 %)	78 (32 %)	25 (31 %)	183 (33 %)
Missing	52 (22 %)	51 (21 %)	26 (32 %)	129 (23 %)
Living area characteristics				
Quintilles Fdep				
[1–3]	138 (59 %)	157 (64 %)	43 (53 %)	338 (60 %)
[4,5]	95 (41 %)	89 (36 %)	38 (47 %)	222 (40 %)
Urban area	150 (64 %)	166 (67 %)	51 (63 %)	367 (66 %)
Local Potential Accessibility to GPs				
< 3.0	53 (23 %)	57 (23 %)	15 (19 %)	125 (22 %)
[3.0–4.0]	68 (29 %)	67 (27 %)	26 (32 %)	161 (29 %)
> 4.0	112 (48 %)	122 (50 %)	40 (49 %)	274 (49 %)
Home-Care facility duration (in min) Median (IQR)	37 (17–73)	27 (15–59)	26 (13–57)	32 (15–64)
Home-Care facility distance (in km) Median (IQR)	41 (13–94)	27 (10–69)	28 (11–70)	33 (11–81)
Health-related characteristics				
Performance status (2 classes)				
0–1	197 (85 %)	200 (82 %)	62 (77 %)	459 (82 %)
2–4	35 (15 %)	45 (18 %)	18 (23 %)	98 (18 %)
Unknown	1 (0 %)	1 (0 %)	1 (0 %)	3 (0 %)
Charlson Comorbidity Index				
0	104 (45 %)	101 (41 %)	28 (35 %)	233 (42 %)
1	31 (13 %)	27 (11 %)	19 (23 %)	77 (14 %)
≥ 2	12 (5 %)	10 (4 %)	1 (1 %)	23 (4 %)
Missing	86 (37 %)	108 (44 %)	33 (41 %)	227 (40 %)
Clinical characteristics				
Ann Arbor stage				
I	20 (9 %)	31 (13 %)	10 (12 %)	61 (11 %)
II	33 (14 %)	33 (13 %)	6 (7 %)	72 (13 %)
III	30 (13 %)	26 (11 %)	12 (15 %)	68 (12 %)
IV	150 (64 %)	156 (63 %)	53 (66 %)	359 (64 %)
Age-adjusted International Prognosis Index				
Low or low intermediate risk	95 (41 %)	111 (45 %)	28 (34 %)	234 (42 %)
High intermediate risk	104 (45 %)	95 (39 %)	33 (41 %)	232 (41 %)
High risk	28 (12 %)	27 (11 %)	13 (16 %)	68 (12 %)
Missing	6 (2 %)	13 (5 %)	7 (9 %)	26 (5 %)
B-symptoms	66 (28 %)	84 (34 %)	36 (44 %)	186 (33 %)
Geriatric assessment				
G8 Median (IQR)	14.00 (11.50–14.50)	14.00 (11.00–15.00)	11.00 (9.00–13.00)	13.00 (10.50–15.00)
Missing	230 (99 %)	39 (16 %)	10 (12 %)	279 (50 %)
G8				
< =14	NA	123 (50 %)	64 (79 %)	NA
> 14	NA	84 (34 %)	7 (9 %)	NA
Missing	NA	39 (16 %)	10 (12 %)	NA

events were combined and let to the following situations: "No treatment/Alive", "No treatment/Died", "Treated/Alive", "Treated/Died", "Unsuccessful treatment/Alive" and "Unsuccessful treatment/Died". The plots stacked theses percentage by month from diagnosis to 1-year and were presented by age (60–69 y/70–79 y/≥80 y).

Overall survival (OS) was described using Kaplan Meier curves. Survival time was calculated from the date of first treatment initiation to the date of death, or to the date of last follow-up (defined as the maximum between any date: treatment, response evaluation, questionnaire completion, follow-up). All-cause mortality was defined as death from any cause. For patients who did not die (i.e. censored), the date of last follow-up was retrieved from clinical consultations, treatment response evaluations, completion of questionnaire or contact with clinicians. 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 (NS) using Pohar-Perme estimator [32]. Net survival is the survival probability that would be observed if the patients can only die from their DLBCL. Despite being a hypothetical quantity, net survival is very useful for comparisons between groups with different background mortality as age groups (or between different countries, etc…). For net survival 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. Finally, a Cox model including age, sex, age adjusted IPI (0–1/2/3/missing) was used to calculate adjusted survival and proportional hazard assumption tested by Schoenfeld residual (data not shown).

Sensitivity analyses, including the 240 patients with home address at diagnosis missing, were performed and are presented in Supplementary Material. First, the main clinical characteristics (Table S1), OS and NS (Fig. S1) are presented according to the availability of the home address. Then, treatment (Table S2), OS and NS are presented according to age groups (Fig. S2).

Analyses were conducted using R software V4.2.1.

3. Results

3.1. Population characteristics

Among the 1205 patients treated for DLBCL and included in the REALYSA cohort between 2018 and 2021, 405 were excluded because they were under 60 years of age at diagnosis, and a 240 additional patients were also excluded because the information of their home address at diagnosis was not available. Thus, 560 were included in the present work. Median of age at diagnosis of this group was 72 years (IQR=67–77). More than half of the patients were males (55 %), married or in a relationship (63 %), living in urban (66 %) and low deprived area (60 %) (Table 1). Patients mainly received secondary education, although nearly 40 % of values were missing. Differences were observed between age groups with a higher proportion of men and individuals in couple among the youngest patients than in the oldest ones. Compared to their younger counterparts, oldest old patients were less graduated from post-secondary education (17 %, 21 %, and 7 % in patients aged 60–69, 70–79, 80 + respectively). Then, a larger part of oldest old patients was living in deprived area at diagnosis compared to younger patients (41 %, 36 %, and 47 % respectively). Regarding duration and distance between home and care facility, the youngest patients experienced longer time (37 min vs 26–27 min) and distance (41 km vs 27–28 km) compared to older patients.

Regarding health condition, a major part of the patients presented with PS 0–1, indicating they were fully active or only restricted in vigorous activity. With increasing age, the proportion of PS 0–1 patients decreased (85 % in patients aged 60–69, 82 % in patients aged 70–79, 78 % in patients aged ≥80). Similar results were observed for CCI, despite a large part of missing information.

Two thirds of patients were diagnosed at advanced stage, i.e. Ann Arbor stage IV, with comparable results between age groups (64 %, 63 %, 65 % in patients aged in patients aged 60–69, 70–79, 80 + respectively). Near half of patients presented high-intermediate of high-risk regarding aaIPI, with a lower proportion of low risk in the oldest old. B-symptoms were more frequent in the oldest old, indicating higher tumor volume and more advanced disease. A larger proportion of the oldest old presented with impaired G8 at diagnosis (79 % compared to 50 % in patients aged 70–79).

3.2. Care management

Less than 60 % of patients aged under 80 received cancer diagnosis and treatment in the same care facility, compared to 54 % in oldest old patients. As expected, the majority of patients were treated with R-CHOP (71%) while 81 % of the oldest patients were treated with R-miniCHOP (Table 2).

Regarding the care pathway (Fig. 1), we observed comparable trends between all age groups. Near half of patients had their first contact in a private clinic. Then, treatment decisions and treatment initiation mainly took place in University Hospital or specialized Cancer Center.

Most patients received treatment and were alive within 3 months of diagnosis (Fig. 2). The proportions of treated patients and still alive at 3 months were 97 % for patients aged < 70, 99 % for those aged 70–80 and 90 % for those aged 80 + . At 1 year, the oldest old had a higher rate of treatment failure (21 % compared to 13 % in patients aged 60–69, and 12 % in patients aged 70–79), regardless of vital status.

3.3. Overall and net survival

Among the 560 patients included in the present work, 53 (9 %) died during the first year following treatment. OS probabilities were 98 %, 97 % and 86 % at 6 months, and 91 %, 95 % and 75 % at 1 year after DLBCL treatment in patients aged 60–69, 70–79, and 80 and older, respectively (Fig. 3). Compared to patients aged 60–69, the oldest old had a lower 1-year OS than their younger counterparts, even after adjustment for sex and IPIaa (HR= 3.2 IC95 %=1.73–5.97).

When considering net survival, which represents the survival that would be observed if DLBCL was the only cause of death, we did not observe any significant differences between age groups.

4. Discussion

In this cohort of older adults diagnosed with DLBCL, we reported differences between the oldest old and their younger counterparts regarding characteristics, care management and survival (Fig. 4).

Overall, the sociodemographic characteristics of our study population reflected the cancer population, with a predominance of males [17, 33], as well as the older population, with a decreasing proportion of men and married individuals when age increased [34]. Compared to their younger counterparts, the oldest old presented more often with altered PS and comorbidities at diagnosis. Similar results were reported in the literature on DLBCL patients [35,36]. Nearly two thirds of the patients were diagnosed at Ann Arbor stage IV in our population, while previous studies reported from 34 % to 63 % of Ann Arbor stage IV in older adults

Table 2
Curative treatment of adults with a diagnosis of DLBCL included in the REALYSA cohort between November 2018 and December 2021 (N = 560).

Curative treatment	60–69 N = 233	70–79 N = 246	≥ 80 N = 81	Overall N = 560
R-CHOP	198 (85 %)	199 (81 %)	3 (3.7 %)	400 (71 %)
R-miniCHOP	2 (0.9 %)	18 (7.3 %)	66 (81 %)	86 (15 %)
Other*	33 (14 %)	29 (12 %)	12 (15 %)	74 (13 %)

n (%);
* other contains 6 missing data.

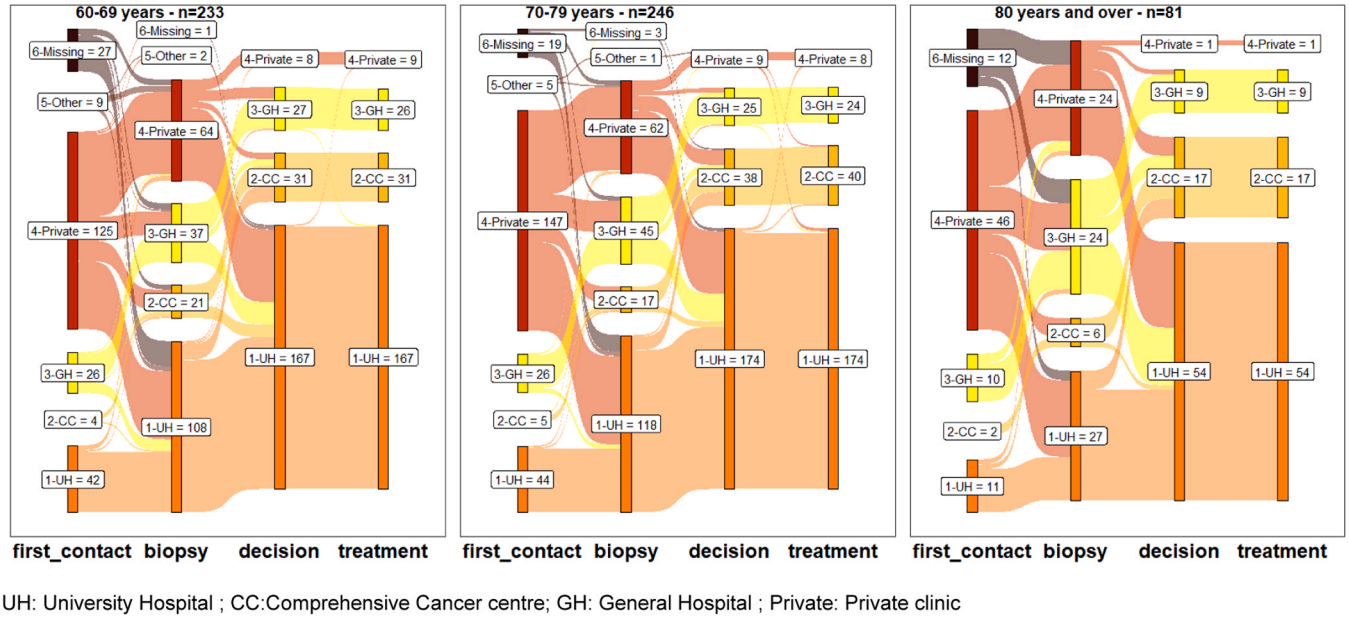

Fig. 1. Care pathway of treated older patients diagnosed with DLBCL from first medical contact to treatment initiation by type of care center and age group, REALYSA study (N = 560). UH: University Hospital; CC:Comprehensive Cancer centre; GH: General Hospital; Private: Private clinic.

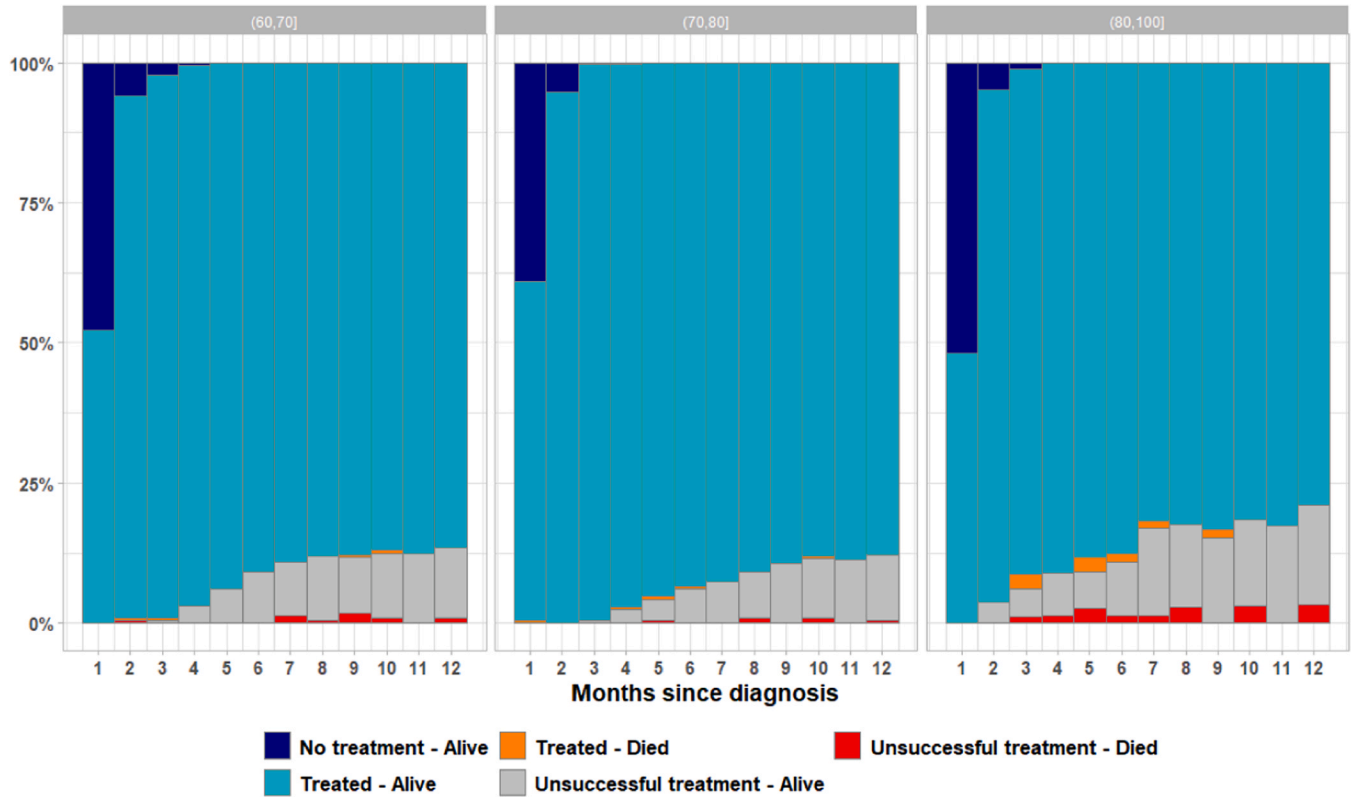

Fig. 2. Distribution of older adults diagnosed with DLBCL regarding treatment administration, progression and vital status by age group in the 12-month after diagnosis, REALYSA study – (N = 560).

with DLBCL [35–38]. A recent study also observed a lower proportion of advanced stage in the oldest old compared to patients aged 65–79 [35], that we did not find in our study population, with similar percentages of stage IV DLBCL between age groups. Oldest old patients presented a slightly higher prognostic risk. Compared to patients aged 70–79, the oldest old mainly presented with an impaired G8 requiring a geriatric assessment. The International Society of Geriatric Oncology (SIOG), as well as the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) recommend performing a geriatric assessment in older adults with cancer in order to guide treatment decision-making and avoid under or overtreatment [39–42]. While geriatric assessment is sometimes considered time-consuming and resource-intensive, although it may be cost-saving [43], screening tools, as the G8, enable screening patients who would benefit from geriatric

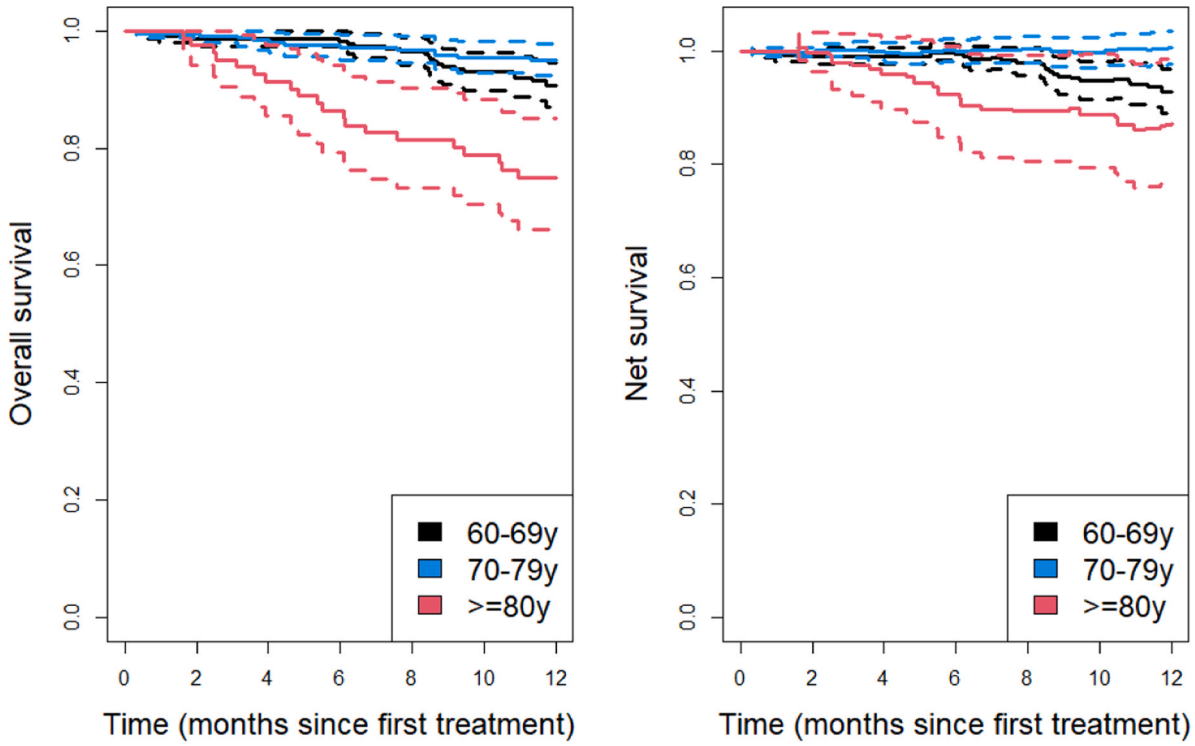

Fig. 3. Overall and net survival in treated older adults diagnosed with DLBCL by age (60–69 y (black)/70–79 y (blue)/≥ 80 y (red)). REALYSA study (N = 560).

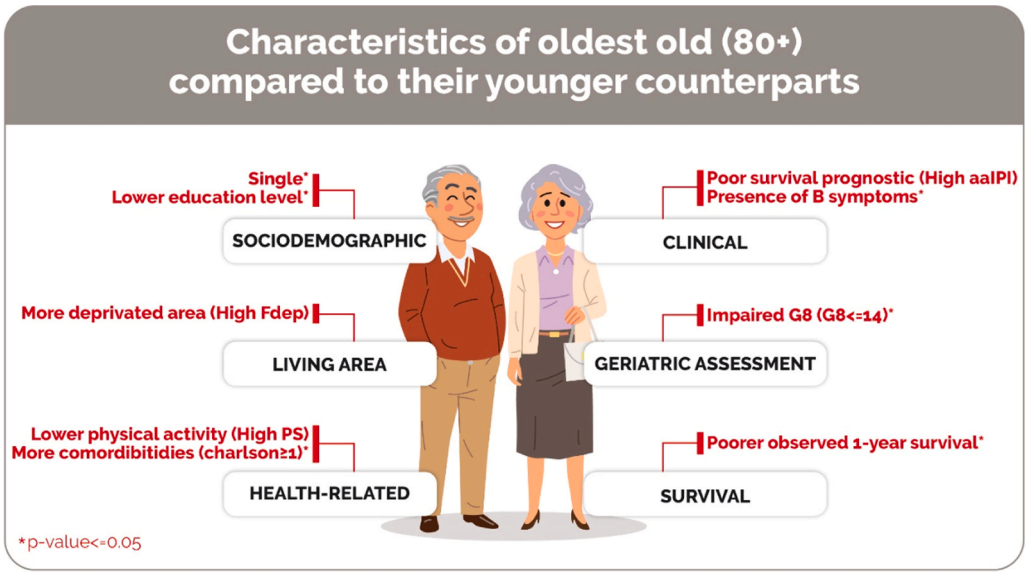

Fig. 4. Synthesis of main differences between the oldest old patients with DLBCL compared to younger patients, REALYSA study.

assessment [31,44]. Unfortunately, in the present work, information on geriatric consultations were not reliable. Thus, we were not able to estimate the proportion of these patients who really benefit from geriatric assessment, as well as the decisions resulting from them. However, a large proportion of patients aged 70 and over was screened for frailty, showing a large adherence to international recommendations on care management in older adults with cancer. These recommendations support the importance of screening for frailty in older adults with cancer, as well as performing a geriatric assessment when needed (e.g. impaired G8). Indeed, even in patients with good PS, geriatric assessment can identify several geriatric impairments. Geriatric assessment enables better treatment decisions by predicting toxicity [45] and less care-related use [46].

In our study population, R-CHOP was the main curative treatment, as recommended for DLBCL [47]. However, the proportion of patients receiving R-CHOP decreased drastically from aged 80; from 81 % in patients aged 70–79–7 % in patients aged 80 and older. The literature suggests that older adults who can tolerate standard therapy for DLBCL, as R-CHOP, experience similar outcomes to those of younger patients [48]. Conversely, frail older adults are better managed with reduce dose therapy as R-mini-CHOP which was demonstrated to be safe and effective treatment for this population [49] [50]. The increasing proportion of impaired G8 with age may explain that the proportion of patients treated by R-miniCHOP also increased with age.

In our population of treated patients with DLBCL, we reported a lower proportion of treatment at 3-month in the oldest old compared to their younger counterparts. These findings may suggest a longer delay between diagnosis and treatment in this population, as supported by a study reporting long delay to treatment initiation in older patients and those with altered PS [51]. This longer delay to treatment initiation could be due to G8 screening and requirement to geriatric assessment. However, patients aged 70–79, in whom 50 % had impaired G8 at diagnosis, were 99 % to receive or have received treatment at 3-month from diagnosis. Our findings also suggested higher treatment failure, including death, in the oldest old. Further research should focus on the delay to treatment initiation, as well as treatment adaptation in the older adults. Indeed, few studies suggest that proportion of the oldest patients can handle standard treatment as R-CHOP vs attenuated immunochemotherapy regimen (R-miniCHOP) [15,38] [52].

In the present work, we reported lower 1-year OS and comparable net survival in the oldest old compared to younger patients with DLBCL. These findings are in line with previous studies [5,13,14,35,53]. We highlighted larger difference between the oldest old and patients younger than 80 in OS than net survival, which was also previously reported. These findings enhance the fact that for older adults groups with different population mortality, net survival can be more appropriate than OS in this context. In our population, we may hypothesize that the large difference in OS may be explained by several factors including PS, comorbidities or social deprivation [8,13]. Regarding net survival, the differences between age groups may find an explanation in the higher rate of treatment failure and toxicities in the oldest old [53].

This study is one of the rare studies based on real-world data dedicated to older adults, with a focus on the oldest old. Older adults are usually excluded to clinical trials [11], and prospective cohort studies are scarce in this population. Thus, this study brings new elements on characteristics, as well as care management and survival in older adults with DLBCL, in particular the oldest old.

However, only treated patients were included in the study, so we were not able to describe patients who did not receive cancer-related treatment and differences between age groups. Studies reported that the oldest old present a lower likelihood to receive curative treatment, despite observations of potential survival benefits in this population when such treatments are administered [54–56]. In addition, due to the REALYSA study design, patients were included through their hematologist, which may explain that no difference were observed regarding the care pathway between the age group, while a study highlighted that oldest patients do not experience the same route to diagnosis than their younger counterparts [35]. REALYSA had been designed to minimize exclusion criteria as compared to interventional clinical trials, and to have the best representativeness of lymphoma practice. However, we acknowledge an overrepresentation of University teaching hospital in this cohort. New analyses are currently performed to contextualize the results obtained on the cohort, especially on representativeness. We recently analyzed the reason of inclusion/non-inclusion in REALYSA cohort in one University hospital during one year [57]. We showed that 56 % of patients were included in REALYSA. This inclusion rate is higher than those usually observed in prospective clinical trials. In this monocentric analysis, patients with an aggressive lymphoma and immediate treatment need had lower inclusion rate. Interestingly we also observed lower inclusion rate in patients with an asymptomatic disease with "watch and wait" strategy [57]. Additional sub-analyses on other centers are ongoing to better understand participation bias in this real-life cohort.

The proportion of oldest old patients in our study was low (14 %). Larger samples are needed to dig into differences regarding characteristics, care management and survival among the older adults, in particular the oldest old which is the fastest-growing group in developed countries. The REALYSA study will enable to study a larger sample of older patients with DLBCL in few years. This larger sample, with a longer follow-up, will also help to better understand the association between older age and patient survival considering more relevant patient characteristics.

Finally, our findings were weakened by some missing data, mainly regarding home address at diagnosis. However, we performed sensitivity analyses including treated older patients with and without an available address, and even if we observed differences in patient characteristics we showed similar results in term of treatment and survival.

5. Conclusions

In this study, we highlighted differences in terms of characteristics, care management and survival between the oldest old patients with DLBCL and their younger counterparts, supporting the need for further work on this specific population. Population-based data are needed in the oldest old to capture the full picture reducing selection bias, to understand the differences between them and younger patients and finally to better explain why treatment innovation in DLBCL doesn't narrow the survival gap between young and older patients.

Funding

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

This specific study was realised during a post doctoral funded by the French Cancer Research Organisation, SIRIC "sites de recherche intégrée sur le cancer" and "La Ligue nationale contre le cancer".

CRediT authorship contribution statement

Monnereau Alain: Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Bijou Fontanet:** Writing – review & editing, Validation. **Galvin Angéline:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Cantrelle Christelle:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Belot Aurélien:** Writing – review & editing, Validation, Methodology, Formal analysis. **Ysebaert Loic:** Writing – review & editing, Writing – original draft. **Peyrou Sandra Le Guyader:** Writing – review & editing, Validation, Supervision, Conceptualization. **Soubeyran Pierre:** Writing – review & editing, Writing – original draft, Validation. **Ghesquières Hervé:** Writing – review & editing, Validation. **Khebbeb Hafirassou Hadia:** Writing – review & editing, Validation. **Fouillet Ludovic:** Writing – review & editing, Validation. **Rossi Cédric:** Writing – review & editing, Validation.

Declaration of Competing Interest

HG has been involved in consultancy and advisory boards for Roche, Gilead, Bristol Myers Squibb(BMS) and AbbVie.

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). They also thank the LYSARC and EPICENE for the administration of the REALYSA database and the provision of data. The authors also thank the investigating centers for their significant contribution to patient recruitment. 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. Finally, the authors thank the patients who participated to the study, whose support and collaboration made the study possible.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2025.102812.

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