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Real-World Data on Lymphoma in Adolescents and Young Adults (AYA)—Report From the Lymphoma and Related Diseases Registry (LaRDR)

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ABSTRACT

Introduction: Lymphoma is a common malignancy among adolescents and young adults (AYAs) which is generally defined as 15–39 years. Relative to other age groups, lymphoma in AYAs remains understudied with heterogeneous treatment options.

Methods: We performed a retrospective review of patients aged 18–60 years in the Australasian Lymphoma and Related Diseases Registry (LaRDR) with new diagnoses of the common subtypes of lymphoma in AYAs between January 2016 and April 2023. The subtypes are classic Hodgkin lymphoma (cHL), diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL) and Burkitt lymphoma (BL). Patient demographics, disease characteristics, treatment and outcome data were collected, and comparisons were made between AYAs (18–39 years) and older adults (OAs) (aged 40–60).

Results: AYAs had higher rates of cHL and PMBCL whereas OAs presented more frequently with DLBCL. AYAs with cHL and PMBCL had higher rates of early-stage and low-risk disease than OAs. In contrast, both AYAs and OAs were more likely to present with advanced-stage DLBCL and BL. AYAs with cHL were more likely to be treated with BEACOPP as compared to OAs who were more commonly treated with ABVD. There was no significant difference in treatment regimens for DLBCL, PMBCL or BL between AYAs and OAs. AYAs with cHL had better overall survival (OS) compared to OAs; specifically, cHL AYAs had better OS and DLBCL AYAs had better progression-free survival (PFS) and OS compared to OAs.

Conclusion: The study provides valuable data on patient and disease characteristics, treatments used and outcomes in AYA compared to OA aged 40–60 years. Registry data such as from LaRDR can help improve treatment standardisation and AYA patient outcomes.

Trial Registration: The authors have confirmed clinical trial registration is not needed for this submission

1 | Background

Cancer in adolescents and young adults (AYAs) is rare with an incidence rate of 334 per 1 million Australians aged 15–24 years [1]. Haematological malignancies, especially mature B-cell lymphomas, constitute a significant proportion of malignancies that occur within AYAs [2] .

Data from the Surveillance, Epidemiology and End Results (SEER) database in the United States shows that 9% of all

lymphomas occur in AYAs. Age-adjusted incidences of classic Hodgkin lymphoma (cHL) and diffuse large B-cell lymphoma (DLBCL) are high in this age group, accounting for 42% and 18% of lymphomas in AYAs, respectively [3]. In Australian AYAs, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) comprise two of the ten most common cancers, accounting for 19% (HL 12.5% and NHL 6.5%) of all AYA cancers (aged 15–24) diagnosed between 2000 and 2009 [4].

However, in high-income countries, lymphoma is still a leading cause of mortality in the AYA population with slower improvement in outcomes compared to both paediatric and older adult (OA) populations [3, 5]. Reasons for this include age-related lymphoma cell biology, delay in diagnosis due to decrease suspicion for malignancy in the younger population, lack of medical insurance, relatively less access to medical healthcare compared to older age groups and AYAs having better baseline making it harder to demonstrate improvement [6]. Data specific to lymphoma in AYA is also limited. In addition, since AYA lymphoma share some disease characteristics as those present in paediatric and OA disease, there is no clear consensus on how to treat AYA lymphoma, thus the management of AYA lymphoma is less standardised and often clinician or institution dependent [2].

Here we report retrospective binational data from the Lymphoma and Related Diseases Registry (LaRDR) on the clinical outcomes of cHL, DLBCL, primary mediastinal B-cell lymphoma (PMBCL) and Burkitt lymphoma (BL) in Australian and New Zealand AYAs. There is variability in the age definition of AYA in literature. A commonly used definition is 15–39 years, as defined by the National Cancer Institute (NCI) [7]. However, other studies have applied different age ranges including 15–24, 15–29 and 15–40 years [4, 8–10]. For our study, we adapted the NCI's definition with a modified lower limit of 18 years due to the inclusion criteria of LaRDR [8].

2 | Methods

Data were extracted from LaRDR, a prospective clinical registry of patients aged ≥ 18 years diagnosed with lymphoma or related diseases [11]. Patients are referred by haematologists and haematology nurses from 31 participating sites across Australia and New Zealand.

2.1 | Patient Selection

Patients aged 18–60 years in the LaRDR with a diagnosis of cHL, DLBCL, PMBCL or BL between January 2016 and April 2023 were included for analysis. T-cell lymphomas were excluded as these are significantly rarer in this population. To compare outcomes, patients were divided into two groups: 'AYA' (aged 18–39) and 'OA' (aged 40–60). Patients over the age of 60 were excluded due to expected significant differences in fitness and clinical characteristics compared to the younger age group.

Demographic information, histological subtype, disease characteristics, treatment regimen and response to therapy were analysed using descriptive statistics. Comparisons of categorical variables were performed using the chi-square test and for continuous variables using the rank-sum test. Histological subtypes in LaRDR are based on the 2016 revision of the World Health Organization classification of lymphoid neoplasms [12]. The Ann Arbor classification is used for staging and the Lugano Criteria for assessing response to therapy [13]. Patients with cHL are risk-stratified with the Hasenclever International Prognostic Score (HIPS) into low (HIPS < 2) or high (HIPS ≥ 2) risk disease [14]. The age-adjusted International Prognostic Index (aaIPI) was used for risk stratification of patients with DLBCL [15].

TABLE 1 | Patient characteristics.

	AYA ($n = 506$)	OA ($n = 526$)	p value
Median age at diagnosis, IQR	29.1 (24.3, 33.9)	51.9 (46.6, 56.3)	
Male sex, n (%)	269/506 (53)	345/526 (66)	< 0.001
Primary diagnosis, n (%)			< 0.001
cHL	343/506 (68)	123/526 (23)	
Mature B-cell NHL	163/506 (32)	403/526 (77)	
DLBCL	92/506 (18)	368/526 (70)	
PMBCL	47/506 (9)	15/526 (3)	
BL	24/506 (5)	20/526 (4)	

Abbreviations: AYA, adolescents and young adults; BL, Burkitt lymphoma; cHL, classic Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell-like; IQR, interquartile range; NHL, non-Hodgkin lymphoma; OA, older adults; PMBCL, primary mediastinal B-cell lymphoma.

Overall survival (OS) and progression-free survival (PFS) were estimated using Kaplan–Meier analysis with survival distributions compared using a log-rank method test. OS was defined as time from diagnosis to death, and PFS as time from diagnosis to death or disease progression. All analyses were done in Stata/MP v17.

Human Research Ethics Committee (HREC) approval was obtained for the LaRDR from Monash Health and all participating sites. Local ethics approval was obtained for the study (2020.LRE.00016). This project was approved by the LaRDR steering committee.

3 | Results

3.1 | Patient and Disease Characteristics

In total, 1032 patients were included for analysis (Table 1). The median age at diagnosis (years) of the AYA and OA groups were 29.1 (interquartile range IQR, 24.3–33.9) and 51.9 (IQR, 46.6–56.3), respectively. There was a higher proportion of males in the OA cohort (66% vs. 53% in AYA, $p < 0.001$). B-cell NHL was more common in OAs (77% vs. 32%), with DLBCL (70%) accounting for most NHL cases, and HL was more common in AYAs (23% of adults vs. 68% AYAs). The most common subtype of lymphoma in AYAs was cHL (68%). DLBCL, PMBCL and BL accounted for 18%, 9.3% and 4.7% of AYA cases, respectively.

TABLE 2 | Classic Hodgkin lymphoma (cHL) disease characteristics.

cHL disease characteristics	AYA ($n = 506$)	OA ($n = 526$)	p value
Staging, *n* (%)			0.003
I/II	189/328 (58)	51/117 (44)	
III/IV	139/328 (42)	66/117 (56)	
HIPS, *n* (%)			< 0.001
Low (0–2)	232/319 (73)	53/111 (48)	
High (3 or more)	87/319 (27)	58/111 (52)	
Histology, *n* (%)			
NS-cHL	161/343 (47)	39/123 (32)	
LR-cHL	4/343 (1)	2/123 (2)	
MC-cHL	17/343 (5)	11/123 (9)	
LD-cHL	0/343 (0)	1/123 (1)	
NOS	161/343 (47)	70/123 (57)	

Abbreviations: AYA, adolescents and young adults; cHL, classic Hodgkin lymphoma; HIPS, Hasenclever International Prognostic Score; LD, lymphocyte-deplete; LR, lymphocyte-rich; MC, mixed-cellularity; NOS, not otherwise specified; NS, nodular sclerosis; OA, older adults.

A higher number of cHL AYA patients presented with early disease (Stage I/II) as compared to OAs (58% vs. 44%, $p = 0.003$) (Table 2). Similarly, more AYA patients had a low HIPS (0–2) as compared to OAs (73% vs. 52%, $p < 0.001$). In both groups, nodular sclerosis cHL (NS-cHL) was the most common histological subtype (47% vs. 32%).

Both AYA and OA DLBCL had similar rates of advanced-stage disease that is Stage III/IV at presentation (57% vs. 60%, $p = 0.73$) (Table 3). There was no significant difference in the aaIPI between the groups with most patients having intermediate-risk disease (AYA vs. OA: 41% vs. 43%, $p = 0.98$). There was no significant difference in the cell-of-origin (COO) between the groups, with similar proportions of germinal centre B-cell-like (GCB) or non-GCB subtypes ($p = 0.14$). There were more cases of PMBCL in AYA (9.3%) than in OA (2.9%). Both groups had similarly high rates of early-stage disease (63% vs. 85%, $p = 0.36$). There was no difference in the incidence of BL in AYA and OA (4.7% vs. 3.8%) and both groups were more likely to present with advanced-stage (III/IV) disease (59% vs. 67%, $p = 0.49$).

3.2 | Treatment Protocols and Outcomes

The main treatment protocols and response rates observed in both groups are summarised in Table 4. A relatively higher proportion of AYAs received escalated-dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) (19% vs. 12% in adults). Meanwhile, more adults received doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) (82% vs. 78% in AYA). There was a higher proportion of males, as well as patients with higher HIPS and advanced-stage disease in AYAs who received BEACOPP as compared to other regimens ($p < 0.001$). In both age groups, most patients with DLBCL received rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP21) (64% vs. 64%). A higher proportion of adults with PMBCL received dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R) as compared to AYAs but this did not reach statistical significance (75% vs. 48%, $p = 0.93$) [16–18]. Similar proportions of adults and AYAs with BL received rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate (R-CODOX-M) (21% vs. 26%) and dose-modified cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide and high-dose cytarabine (dmCODOX-M/IVAC) (25% vs. 26%). There was no significant difference in the use of radiotherapy for either group across lymphoma subtypes.

TABLE 3 | Diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma and Burkitt lymphoma disease characteristics.

NHL disease characteristics	AYA ($n = 506$)	OA ($n = 526$)	p value
DLBCL			
Staging			0.73
I/II	35/82 (43)	125/316 (40)	
III/IV	47/82 (57)	191/316 (60)	
aaIPI			0.98
Low (0)	18/68 (27)	71/259 (27)	
Low-intermediate (1)	18/68 (27)	63/259 (24)	
High-intermediate (2)	28/68 (41)	111/259 (43)	
High (3)	4/68 (6)	14/259 (5)	
Cell-of-origin			0.14
GCB	47/73 (64)	26/73 (36)	
PMBCL			
Staging			0.36
I/II	25/40 (63)	11 (85)	
III/IV	15/40 (38)	2 (15)	
BL			
Staging			0.49
I/II	9/22 (41)	4/15 (27)	
III/IV	13/22 (59)	11/15 (73)	

Abbreviations: AYA, adolescents and young adults; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell-like; NHL, non-Hodgkin lymphoma; OA, older adults; PMBCL, primary mediastinal B-cell lymphoma.

Response rates were similar between the groups across the subtypes. Although a higher proportion of OA patients with PMBCL achieved complete remission (CR) as compared to AYAs, this did not reach statistical significance (90% vs. 68%, $p = 0.34$).

3.3 | OS and PFS

The median follow-up was 16 months. AYAs had better overall OS and PFS compared to OAs ($p < 0.001$) which may be due

TABLE 4 | Treatment protocol and treatment outcomes.

Treatment protocol	AYA ($n = 506$)	OA ($n = 526$)	p value
cHL treatment protocol			0.16
ABVD	231/296 (78)	87/106 (82)	
BEACOPP	56/296 (19)	13/106 (12)	
Other	9/296 (3)	6/106 (6)	
Any radiotherapy	82/343 (24)	34/123 (28)	0.41
cHL response			0.72
CR	241/275 (88)	82/94 (87)	
DLBCL treatment protocol			0.97
R-CHOP21	52/81 (64)	214/333 (64)	
Any radiotherapy	23/92 (25)	66/368 (18)	0.12
DLBCL response			0.35
CR	53/68 (78)	214/290 (74)	
PMBCL treatment protocol			0.093
DA-R-EPOCH	21/44 (48)	9/12 (75)	
Any radiotherapy	12/47 (26)	3/15 (20)	0.66
PMBCL response			0.34
CR	25/37 (68)	9/10 (90)	
BL treatment protocol			0.89
dmCODOX-M/IVAC	6/24 (25)	5/19 (26)	
R-CODOX-M	5/24 (21)	5/19 (26)	
Any radiotherapy	1/24 (4)	1/20 (5)	0.89
BL response			
CR	17/21 (81)	11/13 (85)	0.73

Note: Treatment regimens: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; DA-R-EPOCH, dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; dmCODOX-M/IVAC, dose-modified cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, cytarabine; BEACOPP, escalated-dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; R-CODOX-M, rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate.

Abbreviations: AYA, adolescents and young adults; BL, Burkitt lymphoma; cHL, classic Hodgkin lymphoma; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; OA, older adults; PMBCL, primary mediastinal B-cell lymphoma.

to more patients presenting with early-stage and lower risk disease (Figure 1A,B). There were no observable differences in survival based on sex, either in the cohort as a whole or in histologic subgroups. In sub-group analysis, improved outcomes were noted for AYA patients with cHL or DLBCL (Figure 1C–F).

While AYAs with cHL had better OS than OAs ($p = 0.001$), there was no significant difference in PFS between these groups ($p = 0.80$). AYAs with DLBCL had a better outcome than OAs: the 24-month OS was 91% (95% CI 80–96) and 80% (95% CI 75–85) for AYA and OA, respectively ($p = 0.01$, HR 3.1 (95% CI 1.2–7.7, $p = 0.02$). The 24-month PFS was 84% (95% CI 72–91) and 72% (95% CI 66–77) for AYA and OA, respectively ($p = 0.046$, HR 1.9 (95% CI 1.0–3.5, $p = 0.05$). Sample sizes for BL and PMBCL were too small to draw comparisons between these groups.

4 | Discussion

Our study is the first to report patient and disease-specific characteristics, treatment and outcomes of lymphoma in the AYA population in Australia and New Zealand compared to OAs.

The incidence and distribution of lymphoma subtypes differ by age. Concordant with other studies, we found that AYAs had a higher frequency of cHL whereas OAs had a higher frequency of DLBCL [3]. Overall, there was a higher proportion of male AYAs and OAs within most lymphoma subtypes in our study. In contrast to the study of Blum et al., which reported similar proportion of males in AYAs (15–39 years) and OAs (> 39 years), we noted a higher proportion of males in OAs as compared to AYAs [3].

The Swedish Lymphoma Register investigated population wide sex differences in incidence of lymphoma subtype and mortality in adults aged 18–99 diagnosed in 2000–2019. They reported that men were at higher risk of cHL, DLBCL and BL but expectedly, as shown in our study, not PMBCL where 57% of patients were women [19, 20]. Patients with PMBCL were older and more likely to be female [21].

The reasons for higher risk of lymphoma in younger men is unclear, but possible explanations are differences in sex hormones and immunosurveillance [22, 23]. For example, having full-term pregnancy, especially at a younger age, accounted for most of the reduction in B-cell NHL risk that was observed in the California Teachers Study cohort. It is postulated that prolonged and high-level exposure to progesterone during full-term pregnancies may potentially inhibit development of B-cell NHL [23]. Male sex is also recognised as a negative prognostic marker in HL as listed in the HIPS [14]. Similarly, male sex was reported by Hedstrom et al. to be an adverse risk factor in DLBCL, especially in young patients with an age cut-off of 52 years [24]. The increased mortality in males is hypothesised to reflect differential environmental exposures including viral infection, and/or physiological processes such as sex hormones and immune function [22, 25].

AYAs with cHL in our cohort presented with early-stage and low-risk disease as compared to OAs. It is known that older patients (usually defined as > 50 years) with cHL tend to present with advanced-stage, B symptoms and mixed-cellularity (MC) subtype, all of which combine to result in decreased survival [26, 27]. In contrast, AYAs and OAs with DLBCL in our study had similarly high rates of advanced-stage disease and high-intermediate risk. Concordantly, a retrospective study on AYAs (defined as 16–39 years) had comparably high rates of advanced-stage DLBCL as adults [28]. We found no significant differences in the COO of DLBCL between AYAs and OAs in our cohort, in contrast to other studies which have reported higher rates of GCB in AYAs [29]. Recent studies have

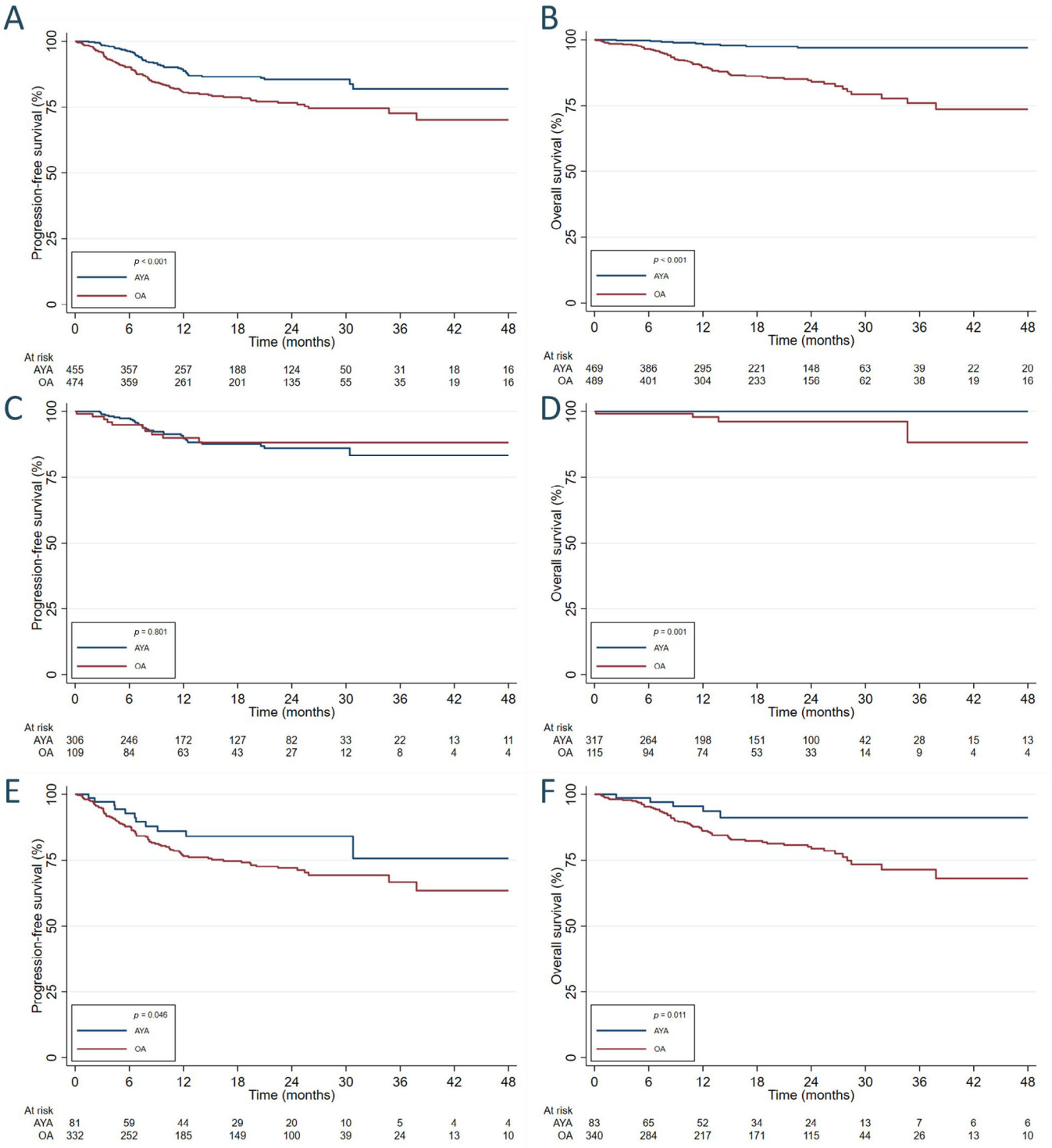

FIGURE 1 | Progression-free survival (PFS) and overall survival (OS) in adolescents and young adults (AYA) versus older adults (OA). (A, B) Kaplan–Meier PFS and OS estimates of patients in the study, with median follow-up of 16 months. (C, D) PFS and OS estimates of patients with classic Hodgkin lymphoma (cHL), with median follow-up of 14 months. (E, F) PFS and OS estimates of patients with diffuse large B-cell lymphoma (DLBCL), with median follow-up of 20 months.

shown that DLBCL can be further classified into distinct genetic subgroups according to next-generation sequencing (NGS) profiles [30]. However, we do not have the relevant data, so we are unable to assess for differences in the genetic subgroups between AYAs and OAs. In our cohort, therefore, differences in the lymphoma cellular biology as assessed by COO cannot explain the difference in the prognosis of DLBCL between AYAs and OAs [6].

We observed predominantly early-stage presentation in PMBCL and a higher frequency of this subtype of lymphoma in AYAs than in OAs. Concordantly, the Swedish Lymphoma Register data

on 172 patients with PMBCL reported a median age of 37.5 years with 67% of patients having early-stage disease [20]. BL, similarly, is reported to occur more commonly in younger patients with a large recent study on 641 patents reporting a median age of 47 years and 36% of patients being < 40 years of age [31]. Late-stage presentation is reported to be more common in BL irrespective of age—this was also noted in our cohort [31]. Our patients with BL mostly had Stage IV disease, consistent with it being a highly aggressive neoplasm.

There were no significant differences in the treatment protocols received by AYAs and OA with cHL in this study. In the AYA group, there were less patients who received BEACOPP as compared to ABVD. However, those who received BEACOPP were more likely to have higher HIPS and advanced-stage disease. There is paucity of data on longer-term treatment-related toxicities (including second malignancies) with BEACOPP in studies which have inclu AYA [32]. Such data will be especially relevant since most AYA lymphoma patients are expected to become long-term survivors with greater life expectancy.

In both AYA and OA groups in our study, R-CHOP21 was commonly used to treat DLBCL. Treatment of DLBCL in AYAs is an area of unmet need with limited data available on outcomes. There have been recent papers comparing adult versus paediatric treatment approaches, with one retrospective study on Canadian AYAs (define as aged 15–21 years) observing benefit from being treated with paediatric protocols [33–35]. We agree with recent papers that there is a need for prospective data in paediatric-based protocols in AYAs with aggressive mature B-NHL, mirroring similar past efforts in acute lymphoblastic leukaemia (ALL) [36, 37].

Our data on the treatment of PMBCL is limited by a small sample size. We found most AYA and OA PMBCL cases were treated with DA-R-EPOCH. In a Swedish register study of 156 PMBCL patients with treatment data available, less than 5% of patients in the Swedish register study were treated with DA-R-EPOCH, with relative survival of 82% [20]. Instead, majority of Swedish patients (58%) were treated with R-CHOEP-14, compared to 2.3% in our study. A recent study has not shown improvement in 4-year EFS compared with historical controls (69.6% vs. 67%, $p = 0.59$ with the use of DA-EPOCH-R in children and adolescents with PMBCL) [38]. As to the use of radiotherapy in PMBCL, this is generally avoided in PMBCL as this disease predominantly affects young females [21]. For patients with treatment data available, 26% of AYA PMBCL in our study received radiotherapy while 17% of patients in the Swedish study had radiotherapy [20]. The optimal treatment of PMBCL in the paediatric and adolescent population has therefore been identified as an area requiring further study, especially as outcomes for this subtype of lymphoma are inferior compared to those of other NHL in this age group [39]. Alternative regimens are required for children and adolescents to have similar survival outcomes observed in adults.

For BL, most patients in our cohort were treated with CODOX-based chemotherapy as standard NHL chemotherapy like R-CHOP has been shown to be inadequate for treating BL [40]. Optimal initial therapy of BL in AYA is unclear with some centres following paediatric protocols. R-CODOX-/IVAC protocol remains frequently used outside of a clinical trial with similar numbers of patients being treated with R-CODOX and R-CODOX/IVAC [41].

Both OS and PFS were superior in the overall AYA cohort compared to OAs in our study, which may reflect the different diagnoses profiles between the two groups. In addition, more AYAs had early-stage and lower-risk disease as compared to OA. Hence, a limitation of this study is the paucity of outcomes adjusted for these differences.

Although AYAs with cHL had early-stage and more favourable prognosis, this did not confer a better PFS compared to OA. Limited data at follow-up may be why there was no statistical differences in cHL PFS even though a large difference in survival curves were noted. The higher proportion of Stage I/II disease may contribute to the better OS of AYA cHL. Overall, the OS and PFS seen in our AYA cohort with cHL is comparable to data from recent studies [42, 43]. Interestingly, despite similar disease features, AYA with DLBCL had better survival compared to OA. This is unlikely to be explained by difference in disease biology or treatment as this was similar in both groups of our study. Within the limitations of a small dataset, difference in GCB proportions was not statistically significant in the two age groups in our cohort. The reported frequency of GCB subtype DLBCL in adult and paediatric populations in other studies are 50% and 75%–82%, respectively [29, 44]. Our study observed a comparable frequency of GCB DLBCL cases in the OA cohort; whereas the GCB frequency in our AYA sits between the OA and paediatric numbers reported in the BFM and FAB studies [29, 44]. This may represent a shift in the disease biology with increasing age. Future studies may identify disease biology unique to AYA that may help in tailoring therapeutic regimens and improving survival. In our AYA cohort, the lowest CR, OS and 24-month PFS was seen with PMBCL as compared to other lymphomas. We were not able to address comparison of outcomes with various treatment regimens because of sample size.

Despite being limited by short follow-up duration and retrospective data, our study provides valuable data on patient and disease characteristics, treatments used and outcomes in AYA compared to OA aged 40–60 years. As the registry continues to expand, representation from rural and regional sites will further increase, and the data will become increasingly representative of the greater Australian context. Registry data will help with improving AYA patient outcomes and treatment standardisation. Moreover, longer follow-up will allow determination of long-term toxicities of treatment in this cohort of patients.

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Conflicts of Interest

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Data Availability Statement

All data analysed during this study are included in this article. Enquiries about data access should be made to the corresponding author.

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