Hindawi
European Journal of Cancer Care
Volume 2023, Article ID 8600327, 12 pages
https://doi.org/10.1155/2023/8600327

Research Article

Treatment and Survival in Acute Leukemia: A New South Wales Study Comparing Adolescents and Young Adults with Children and Adults

Ming Li,[1,2] **Antoinette Anazodo**,[3,4,5,6] **Luciano Dalla-Pozza**,[7] **Paola Kabalan Baeza**,[8] **David Roder**,[1,2] **and David Currow**[9]

[1]*Cancer Institute NSW, Sydney, Australia*
[2]*University of South Australia, Adelaide, Australia*
[3]*School of Women's and Children's Health, University of New South Wales, Randwick, Australia*
[4]*Kids Cancer Centre, Sydney, Australia*
[5]*Sydney Children's Hospital, Randwick, Australia*
[6]*Nelune Comprehensive Cancer Centre, Prince of Wales Hospital for Children, Westmead Hospital, Westmead, Australia*
[7]*Cancer Centre for Children, The Children's Hospital at Westmead, Westmead, Australia*
[8]*Hunter and Northern New South Wales Youth Cancer Service, Calvary Mater Newcastle, Australia*
[9]*Faculty of Science, Medicine and Health, University of Wollongong, Wollongong NSW, Sydney, Australia*

Correspondence should be addressed to Ming Li; ming.li@unisa.edu.au

Received 13 October 2022; Revised 18 December 2022; Accepted 20 December 2022; Published 9 February 2023

Academic Editor: Lalit Batra

Objective. To investigate age differences in treatment and survival from acute lymphoblastic (ALL) and acute myeloid leukemia (AML). *Methods*. 1053 ALL/566 AML patients diagnosed in 2003–2015 on the New South Wales Cancer Registry were included. Treatment within 12 months from diagnosis was assessed using linked registry, hospital, and health-insurance data. Differences by age at diagnosis in treatment and survival were investigated using socio-demographically adjusted regression analyses, with adolescents and young adults (AYA, 15–24 years) as the reference category. *Results*. Children were less likely than AYA to start ALL treatment >3 days from diagnosis (adjusted odds ratio (aOR 0.39, 95% CI 0.27–0.57)) and to have multiple treatment types (aOR 0.22, 95% CI 0.14–0.34). For AML, aOR of treatment start >3 days was 0.16 (95% CI 0.09–0.29) for children compared with AYA, with no age differences in treatment types. Five-year disease-specific survival for ALL was 84%. Children were less likely than AYA to die from ALL (adjusted subhazard ratio (aSHR 0.32, 95% CI 0.22–0.50)). For AML, the corresponding survival was 73% without an age difference. Children having multiple treatment types for ALL had an increased risk of mortality at aSHR 2.67 (95% CI 1.53–4.67), but not adults at 1.26 (95% CI 0.67–2.47) (interaction $p = 0.017$). Time from diagnosis to initial treatment start and initial treatment type were not associated with mortality outcomes after adjusting for socio-demographic variables. *Conclusion*. Children with ALL had better survival. ALL Mortality were negatively associated with multiple treatment types.

1. Introduction

Acute leukemias are common in children, adolescents, and young adults, where they are a major source of trauma for affected families [1]. They are broadly categorised as acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) [2]. Globally, leukemia constituted the highest proportion of cancers, and more than one-third (34%) of all childhood cancer Disability-AdjustedLife-Years (DALYs) was attributable to leukemia in 2017 [3]. In Australia, ALL and AML accounted for the 5th leading cancer burden for cancers following melanoma, gonadal germ cell cancer, Hodgkin lymphoma, and thyroid carcinoma accounting for 7.2% of new cases in 2010–2014 for ages 15–24 years [2]. In NSW, the largest state in Australia, ALL and AML accounted for 30.4% and

5.8%, respectively, of cancers diagnosed in children in 2003–2015, compared to 4.4 and 3.6%, respectively, in adolescents and young adults [4].

The causal attribution of acute leukemia is uncertain, but it is likely that abnormal genes and immune system responses play a role. Risk factors associated with leukemia include genetic, infectious, and environmental influences. These include, for example, family history, having certain genetic disorders (Down Syndrome), exposure to ionizing radiation, hydrocarbons and pesticides, alcohol, cigarette smoking, and illicit drug use [5–7]. In recent decades, substantial increases in 5-year relative survival have been achieved in young Australians, both for ALL and AML [2]. In children aged 0–14 years, AML survival approximately doubled from 39% in 1986–1991 to 77% in 2010–2015 [8], although it remained substantially lower than for ALL which ranged from 76% in 1986–1991 to 92% in 2010–2015. Among adolescents and young adults (AYAs) aged 15–24 years, 5-year-relative survival for ALL increased from 33% in 1985–1989 to 79% in 2010–2014, while for AML the increase was from 33% to 77% [2].

The increases in survival from acute leukemias in childhood are mostly attributed to advances in treatment and diagnostic technology [1, 9]. Acute leukemia treatment mainly comprises chemotherapy and bone marrow transplantation, sometimes with added radiotherapy [10]. Increasingly, more intensive leukemia treatments modelled on paediatric regimens are administered to AYAs and adults aged 25–39 years [11–13]. In addition, supportive care plays an important role in preventing and managing symptoms and in addressing treatment complications. It can include facilitating access to treatment, knowledge dissemination, and emotional and health support for families and other carers [14].

Greater attention has also been given to AYA care through Australian Youth Cancer Services (YCS) since 2010, with the aim of drawing on paediatric and young adult clinical services to achieve better integration of AYA cancer care. Increasingly, AYA care delivery has been supported by YCS services [15].

Earlier analyses indicated that AYAs and adults aged 25–39 in NSW had a 48% and 71% higher risk of overall cancer mortality, respectively, when compared with children, which was largely contributed by acute leukemias [4]. Age disparity in treatment has not been well defined at a population level in Australia, nor the extent to which treatment differences have contributed to the lower leukemia survival observed with increasing age.

The purpose of this study was: (1) to examine broad differences in acute leukemia (ALL and AML) treatment-related items among children (0–14 years), AYAs, and adults (25–39 years); (2) to assess associations of these differences with mortality; and (3) to determine the utility of linked data for pursuing these objectives.

2. Methods

2.1. Data Sources and Participants. The study population comprised patients aged 0–39 years diagnosed with ALL ($n = 1053$) and AML ($n = 566$) in 2003–2015 and recorded in the population-based NSW Cancer Registry.

Cancer Registry data were collected under a mandate conferred through the NSW Public and the Cancer Institute (NSW) Act 2003, in accordance with international registry standards [16, 17]. The Registry is administered by Cancer Institute NSW, which is the NSW Government's agency responsible for oversighting cancer control in NSW and providing data support for service planning, funding, management, and evaluation.

Treatment data were mostly extracted from hospital inpatient databases and universal health insurance claims (i.e., claims under the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS)). Hospital data items included dates of admission and clinical procedure codes. Collectively, data from these sources covered most treatments, with MBS and PBS subsidising privately funded hospital and community treatments, and costs of drugs [18, 19].

Linkage was performed by the Centre for Health Record Linkage for NSW-based datasets using probabilistic matching and by the Australian Institute of Health and Welfare for Commonwealth-based data. After linkage, deidentified data were stored in the Secure Unified Research Environment (SURE) facility, a purpose-built remote access computing environment [20]. The number of registered cases that were linked with cancer treatments is shown in Supplementary Figure.

2.2. Data Collection and Classification. The NSW Cancer Registry records the primary cancer site, morphology, diagnosis date, residential area (used to derive socio-demographic characteristics), death date, and cause [21]. The NSW Registry of Births, Deaths, and Marriages, the Australian Bureau of Statistics (ABS), and the National Death Index (NDI) were the sources of death data, both for cancer and noncancer causes [22].

ALL and AML were classified using the International Classification of Diseases for Oncology (ICD-O-3), as employed by the Australian Institute of Health and Welfare [2]. For example, ALL had histology codes of 9811–9818, 9826, and 9835–9837 [2]. Access to death dates and causes were available for the period to December 31st, 2015.

Age in years at diagnosis was categorised as children (0–14 years), AYA (15–24 years), or adult (25–39 years) [23]. Other descriptive variables included sex and diagnostic year, defined as 2003–2007, 2008–2012, and 2013–2015. The residential area was classified as a major city, inner regional, outer regional, or remote/very remote area, using the Australian Standard Geographical Classification Remoteness Index [24]. Socio-economic status was determined by place of residence at the census collector district level and coded using the Socio-Economic Index for Areas (SEIFA), which classifies areas by Index of Relative Socio-economic Disadvantage in quintiles [25]. Country of birth was defined as Australia, other mainly English-speaking countries, or other mainly non-English-speaking countries, as described previously [26].

Treatment-related items include the date of initial treatment start following diagnosis, initial treatment type, and treatment occurring within 12 months from diagnosis.

While the principal treatment was chemotherapy, bone marrow transplantation (BMT) including allogeneic and autologous types, and radiotherapy including total body, cranial radiation, or both were also provided. Initial treatment start was categorised as "within 3 days" vs ">3 days," consistent with our previous research [4] and Cancer Council optimal care guidance [27]. Treatment type was grouped as "chemotherapy only vs multiple treatment types defined as chemotherapy plus other treatment(s)." The 12-month window was used to assess postdiagnostic treatment to align with our previous AYA study [4], other Australian cancer registry studies, and USA CDC Comparative Effectiveness data [28].

Data sources include (a) for systemic therapy-inpatient + PBS + MBS, (b) for BMT—inpatient, and (c) for radiotherapy—inpatient + MBS. Codes for these treatments were those specified in the 10th Revision of the Australian Classification of Health Interventions (ACHI) and the MBS and PBS coding systems [18, 19, 29].

2.3. Statistical Analysis. Sociodemographic and treatment items were compared by age for ALL and AML separately using the Pearson chi-square test, substituting Fisher's exact test for small numbers [30]. Adjusted odds ratios with 95% confidence intervals (aOR, 95% CI) for treatment items were derived using multivariate logistic regression, adjusting for sex, diagnostic period, country of birth, residential remoteness, and SEIFA status [30], with the AYA age group as the reference category.

Kaplan–Meier disease-specificproduct-limit estimates (survival) were calculated in days for ALL and AML. Adjusted subhazard ratios with 95% CIs (aSHRs, 95% CIs) for death from leukemia were calculated by treatment items, adjusting for age, sex, and sociodemographic characteristics, using multivariate competing risk regression with other causes of death interpreted as the competing events [31].

In addition, sensitivity analysis was conducted by excluding those residing in border health districts in NSW (Northern NSW, Albury, Far West, Murrumbidgee, and Southern NSW) who might seek treatment in adjoining states that were outside the scope of NSW data collection. Country of birth was classified using the Human Development Index (developing vs developed country to compare with our past research using the Australian Bureau of Statistics classification [4].

STATA release 16 was used for all analyses [32].

3. Results

3.1. Patient Characteristics. Table 1 summarizes the age differences in patient characteristics by ALL and AML separately.

Of the 1053 people diagnosed with ALL in 2003–2015: 761 (72%) were aged 0–14 years at diagnosis; 162 (15%) were aged 15–24 years; 130 (12%) were aged 25–39 years. A total of 611 (58%) were males; 920 (87%) were born in Australia; 790 (75%) lived in major cities, and 267 (25%) were diagnosed in 2013–2015. By the end of 2015, 159 (15%) had died of ALL.

Among people diagnosed with ALL, characteristics and outcomes varied as follows by age category: sex ($p = 0.036$), with the proportion of males highest for AYAs (67%) and lowest for children (56%); country of birth ($p < 0.001$), with the proportion for Australian-born highest for children (93%) and lowest for older adults (65%) ($p < 0.001$); for survival outcome, with the proportion alive at the end of 2015 highest for children (88%) and lowest for adults (61%) ($p < 0.001$). There was no difference by age category in residential remoteness, SEIFA quintile, or diagnosis period ($p \geq 0.359$).

Of the 566 people diagnosed with AML in 2003–2015: 149 (26%) were children; 129 (23%) were AYAs; 288 (51%) were adults; 317 (56%) were males; 430 (76%) were Australian born, and 438 (77%) lived in major cities. By the end of 2015, 153 (27%) had died of AML.

Among people diagnosed with AML, the only country of birth varied by age category ($p < 0.001$), with Australian-born being most common for children (93%) and least common for adults (64%). No age differences were evident for sex, residential remoteness, SEIFA quintile, or diagnosis period ($p \geq 0.535$). Also, vital status did not vary by age ($p = 0.520$).

3.2. Treatment Related Items. Table 2 summarizes the age differences in treatment items (time to initial treatment start and treatment type) by ALL and AML separately.

3.2.1. Time to Initial Treatment Start and Initial Treatment Type. Of the 1053 ALL and 566 AML cases recorded on the NSW Cancer Registry, 1031 and 505 had linked treatment records.

For people with ALL, the median interval from diagnosis to treatment start was less than one day for children, 12.5 days for AYAs, and 12.0 days for adults. The corresponding proportions starting treatment within 3 days of diagnosis were 63%, 40%, and 30%, respectively, ($p < 0.001$). Of the 152 AYA patients with ALL, 31 were treated at a paediatric centre and started initial treatment within a median of 3 days (IQR 0–15 days) while the remaining 121 patients did so within a median of 16 days (IQR 0–39 days; $p < 0.001$).

For the 505 people with AML, the median time from diagnosis to treatment start was less than one day for children, 39 days for AYAs, and 43 days for ages adults, and the corresponding percentages starting treatment within 3 days was 64%, 23%, and 19%, respectively, ($p < 0.001$). Of the 115 AYA patients with AML, 12 were treated at a paediatric centre, starting their treatment with a median of 2.5 days (IQR 0–35.5 days) from diagnosis, with the remaining 103 patients treated at adult centres having a longer median time to treatment start of 41 days (IQR 8–111 days; $p < 0.001$).

Table 1: Characteristics of patients with ALL and AML by age in NSW cancer registry, 2003–2015.

	ALL ($N = 1053$)				AML ($N = 566$)			
	0–14 ($n = 761$)	15–24 ($n = 162$)	25–39 ($n = 130$)	P^*	0–14 ($n = 149$)	15–24 ($n = 129$)	25–39 ($n = 288$)	P^*
Sex				0.036				0.535
Female	336 (44.2)	54 (33.3)	52 (40.0)		62 (41.6)	62 (48.1)	125 (43.4)	
Male	425 (55.9)	108 (66.7)	78 (60.0)		87 (58.4)	67 (51.9)	163 (56.6)	
Country of birth				<0.001				<0.001
Australia	707 (92.9)	129 (79.6)	84 (64.6)		138 (92.6)	108 (83.7)	184 (63.9)	
Other English-speaking	20 (2.6)	9 (5.6)	10 (7.7)		4 (2.7)	5 (3.9)	14 (4.9)	
Non-English-speaking	31 (4.1)	24 (14.8)	36 (27.7)		5 (3.4)	16 (12.4)	80 (27.8)	
Unknown	3 (0.4)	0 (0)	0 (0)		2 (1.3)	0 (0)	10 (3.5)	
Residential remoteness				0.995				0.753
Major cities	570 (74.9)	122 (75.3)	98 (75.4)		115 (77.2)	96 (74.4)	227 (78.8)	
Inner region	137 (18.0)	30 (18.5)	23 (17.7)		24 (16.1)	26 (20.2)	43 (14.9)	
Outer region and remote	54 (7.1)	10 (6.2)	9 (6.9)		10 (6.7)	7 (5.4)	18 (6.3)	
SEIFA quintiles				0.987				0.637
1st (most disadvantaged)	139 (18.3)	26 (16.1)	21 (16.2)		23 (15.4)	31 (24.0)	60 (20.8)	
2nd	134 (17.6)	27 (16.7)	24 (18.5)		39 (26.2)	27 (20.9)	67 (23.3)	
3rd	186 (24.4)	36 (22.2)	31 (23.9)		30 (20.1)	23 (17.8)	60 (20.8)	
4th	151 (19.8)	34 (21.0)	27 (20.8)		24 (16.1)	22 (17.1)	47 (16.3)	
5th (least disadvantaged)	150 (19.7)	39 (24.1)	27 (20.8)		33 (22.2)	25 (19.4)	54 (18.8)	
Unknown	1 (0.1)	0 (0)	0 (0)		0	1 (0.8)	0 (0)	
Diagnosis period				0.359				0.976
2003–2007	283 (37.2)	57 (35.2)	46 (35.4)		56 (37.6)	48 (37.1)	102 (35.4)	
2008–2012	297 (39.0)	60 (37.0)	43 (33.1)		57 (38.6)	52 (40.1)	114 (39.6)	
2013–2015	181 (23.8)	45 (27.8)	41 (31.5)		36 (24.2)	29 (22.5)	72 (25.0)	
Vital status on 31st Dec. 2015				<0.001				0.520
Alive	672 (88.3)	117 (72.2)	79 (60.8)		113 (75.8)	90 (69.8)	197 (68.4)	
Died of leukemia	77 (10.1)	42 (25.9)	40 (30.8)		33 (22.2)	35 (27.1)	85 (29.5)	
Died of other causes other than leukemia	12 (1.6)	3 (1.9)	11 (8.5)		3 (2.0)	4 (3.1)	6 (2.1)	

Numbers in the table: case number (%). P^* from the Chi-square test (or Fisher's exact chi-square test when a cell count <5) excluding "unknown." Abbreviations: SEIFA: socio-economic index for areas; ALL: acute lymphoid leukemia; AML: acute myeloid leukemia.

Table 2: Treatment history among patients with ALL and AML by age in NSW, 2003–2015.

	ALL				AML			
Cases with clinical records	0–14 years ($n = 754$)	15–24 years ($n = 152$)	25–39 years ($n = 125$)	P^*	0–14 years ($n = 141$)	15–24 years ($n = 115$)	25–39 years ($n = 249$)	P^*
Days from diagnosis to treatment start median (IQR)	1 (0–10)	12.5 (0–32)	12.0 (1–40)	0.001	0 (0–19)	39 (4–84)	43 (12–97)	0.001
Time to treatment start				<0.001				<0.001
Within 3 days	475 (63.0)	61 (40.1)	38 (30.4)		90 (63.8)	26 (22.6)	48 (19.3)	
>3 days	279 (37.0)	91 (59.9)	87 (69.6)		51 (36.2)	89 (77.4)	201 (80.7)	
Initial cancer treatment			0.001				0.007	
Chemotherapy	754 (100.0)	151 (99.3)	122 (97.6)		141 (100.0)	105 (91.3)	227 (91.2)	
BMT	0 (0)	0 (0)	1 (0.8)		0 (0)	4 (3.5)	12 (4.8)	
Radiotherapy	0 (0)	1 (0.7)	2 (1.6)		0 (0)	6 (5.2)	10 (4.0)	
Having cancer treatment within 12 month following diagnosis				<0.001				0.024
Yes	750 (98.6)	150 (92.6)	123 (94.6)		137 (92.0)	111 (86.1)	237 (82.3)	
No	11 (1.5)	12 (7.4)	7 (5.4)		12 (8.1)	18 (14.0)	51 (17.7)	
Treatment type within 12 months following diagnosis				<0.001				0.113
Chemo only	672 (89.6)	100 (66.7)	61 (49.6)		93 (67.9)	66 (59.5)	145 (61.2)	
Radio only	0 (0)	0 (0)	2 (1.6)		0 (0)	4 (3.6)	5 (2.1)	
BMT only	0 (0)	0 (0)	0 (0)		0 (0)	2 (1.8)	3 (1.3)	
Chemo + radio	64 (8.5)	35 (23.3)	44 (35.8)		8 (5.8)	15 (13.5)	28 (11.8)	
Chemo + BMT	12 (1.6)	10 (6.7)	14 (11.4)		36 (26.3)	24 (21.6)	53 (22.4)	
Chemo + radio + BMT	2 (0.3)	5 (3.3)	2 (1.6)		0 (0)	0 (0)	3 (1.3)	
Treatment regimen				<0.001				0.316
Chemotherapy only	672 (89.6)	100 (66.7)	61 (49.5)		93 (67.9)	66 (59.5)	145 (61.2)	
Chemotherapy + BMT/radio	78 (10.4)	50 (33.3)	62 (50.4)		44 (32.1)	45 (40.5)	92 (38.8)	

Numbers in the table: case number (%). Data from linked treatment record. P^* from Kruskal Wallis test for "Days from diagnosis to treatment start median (IQR)"; P from chi-square test (or Fisher's exact chi-square test when a cell count <5) for the others. Abbreviations: ALL: acute lymphoid leukemia; AML: acute myeloid leukemia; IQR: interquartile range; BMT: bone marrow transplant.

For all ages combined, the odds of a later treatment start (>3 days) were higher for ALL cases residing in outer regional and remote areas compared with those living in major cities (aOR 2.26, 95% CI 1.31–3.19). No corresponding difference by remoteness was observed for AML.

Patients diagnosed in the most recent period were more likely to start initial treatment later (>3 days), with the aOR (95% CI) of diagnosis in 2013–2015 being 2.77 (1.97–3.89) for ALL and 2.77 (1.57–4.87) for AML compared with 2003–2007.

Results for time to treatment start were not found to differ in sensitivity analyses when excluding cases (73 ALL and 48 AML) residing in local health districts adjacent to the NSW border (Northern NSW, Albury, Far West, Murrumbidgee, and Southern NSW).

Among people with ALL, all children (100%) had chemotherapy initially, higher than the proportions for AYAs (99%) and adults (98%) ($p = 0.001$); while for AML cases, all children (100%) had chemotherapy initially, compared with lower proportions for AYAs and adults (both 91%; $p = 0.007$).

3.2.2. Treatment within 12 Months following Diagnosis. A total of 1023/1031 (99.2%) people with ALL and 485/505 (96.0%) people with AML had documented evidence of having received antileukemia therapy within 12 months following diagnosis.

Among people with ALL, the proportion having treatment within 12 months in children (99%) was significantly higher than for AYAs (93%) and adults (95%) ($p < 0.001$); Regarding the treatment types used for ALL, 90% of children had chemotherapy exclusively, which was higher than for AYAs (67%) and adults (50%). For AYAs, 23% had chemotherapy plus radiotherapy, while for adults, the third most common anticancer treatment was chemotherapy plus BMT (11%). Treatment type within 12 months from diagnosis for ALL did not differ by sex, country of birth, residential remoteness, socioeconomic status, or diagnosis period.

Among people with AML, the proportion having treatment within 12 months was 92% for children, which was higher than for AYAs (86%) and adults (82%) ($p = 0.024$). The proportion of patients in the different age groups undergoing therapy was similar across the treatment groupings, with chemotherapy (alone) being the most common treatment (68% in children, 60% in AYAs, and 61% in adults), followed by chemotherapy combined with BMT for all age groups (26% in children, 22% in 15–24 years, and 22% for adults).

3.2.3. Assessment of Age Disparity in Treatment Items. The unadjusted and adjusted ORs (95% CI) of treatment items with age are summarized in Table 3.

Compared with AYAs, children with ALL and AML had a 61% (aOR 0.39, 95% CI 0.27–0.57) and 84% (aOR 0.16, 95% CI 0.09–0.29) lower odds of starting treatment later respectively (>3 days following diagnosis). Times to treatment start for adults did not differ from the corresponding times for AYAs (Table 3), after adjusting for sex, country of birth, residential remoteness, socioeconomic status, and diagnosis period.

Compared to AYAs, children had 83% lower odds of not recording treatment for ALL (aOR 0.17, 95% CI 0.07–0.42) in the 12 months from diagnosis, while the corresponding adjusted OR (95% CI) of not recording treatment for AML in children was not statistically significant at 0.53 (0.24–1.16).

Compared to AYAs, the adjusted odds ratio (95% CI) for having combined modality treatment for ALL was 0.22 (0.14–0.34) for children and 2.21 (1.34–3.68) for adults.

3.3. 5-Year Survival and Mortality. On 31st Dec. 2015, 868 (82.4%) people with ALL and 400 (70.7%) with AML were still alive. The proportion surviving for ALL and AML in children was 88.3% and 75.3%, respectively, which was significantly higher than for other age groups.

The overall 5-year leukemia-specific survival after diagnosis was 83.7% for ALL and 72.9% for AML. For ALL, it was 89.2% for children, 72.2% for AYAs, and 65.0% for adults, whereas the corresponding leukemia-specific survivals for AML were 78.8%, 71.4%, and 70.4%. Compared with AYAs, children were 66% less likely to die from ALL (aSHR 0.34, 95% CI 0.23–0.50), whereas the risk of ALL mortality for adults did not differ significantly from that for AYAs (aSHR 1.23, 95% CI 0.79–1.91). There was no age disparity observed in AML mortality risk.

Mortality risk for either ALL or AML did not differ by sex, country of birth, residential remoteness, or diagnosis period, except for a lower mortality risk for ALL patients from the least socioeconomically disadvantaged compared with the most disadvantaged cases (aSHR 0.56, 95% CI 0.32–0.98).

The temporal trend of 5-yearcancer-specific survival for ALL or AML by age groups followed different patterns. The linear trends in survival in children and adults were stable while marked increases occurred for AYAs. Meanwhile, the 5-year survival in children was consistently higher than for AYAs and adults (Figure 1). For example, the 5-year survival from ALL in children increased slightly from 88% for cases diagnosed in 2003–2007 to 91% for those diagnosed in 2008–2010, while for AYAs, it increased more sharply from 72% to 83%, and for adults, from 65% to 69%. The 5-year survival from AML in children remained unchanged at approximately 80% for all cases diagnosed during 2003–2010, while for AYAs, it increased from 60% for cases diagnosed in 2003–2007 to 79% in 2008–2010. For adults, survival was unchanged: 71% for diagnoses in 2003–2007 and 70% for diagnoses in 2008–2010.

3.4. Association between Leukemia Treatment and the Risk of Mortality in 0–39 Years. Table 4 showed the 5-year overall survival of patients with ALL and AML and its associations with treatment items including time to initial treatment, initial treatment with chemotherapy, treatment status, and treatment types in the 12 months after diagnosis.

People with ALL starting treatment within 3 days following diagnosis had a 5-year survival of 85.6%, which was marginally higher than the 82.0% for those starting beyond

Table 3: Age disparity in treatment items (OR[a], 95% CI) among patients with ALL and AML in NSW, 2003–2015.

	ALL			AML		
	0–14	15–24	25–39	0–14	15–24	25–39
Later (>3 days) initial treatment start						
Unadjusted	0.39 (0.28–0.56)	1.00	1.53 (0.93–2.53)	0.17 (0.09–0.29)	1.00	1.22 (0.71–2.10)
Adjusted[b]	0.39 (0.27–0.57)	1.00	1.47 (0.87–2.48)	0.16 (0.09–0.29)	1.00	0.88 (0.57–1.34)
Lacking treatment within 12 month following diagnosis						
Unadjusted	0.18 (0.08–0.42)	1.00	0.71 (0.27–1.86)	0.54 (0.25–1.16)	1.00	1.33 (0.74–2.38)
Adjusted[b]	0.17 (0.07–0.42)	1.00	0.58 (0.21–1.62)	0.53 (0.24–1.16)	1.00	1.14 (0.62–2.11)
Having chemotherapy + BMT/radiotherapy within 12 month following diagnosis						
Unadjusted	0.23 (0.15–0.35)	1.00	2.03 (1.25–3.32)	0.69 (0.41–1.17)	1.00	0.93 (0.59–1.47)
Adjusted[b]	0.22 (0.14–0.34)	1.00	2.21 (1.34–3.68)	0.69 (0.40–1.18)	1.00	0.99 (0.61–1.61)

[a]OR: odds ratio from logistic regression analyses using 15–24-year group as reference. Outcomes were: later initial treatment start (initial treatment start >3 days vs ≤3 days), lacking treatment within 12 months following diagnosis (vs having treatment), and having chemotherapy and other treatment within 12 months following diagnosis (vs having chemotherapy only). [b]adjusted for sex, country of birth, residential remoteness, SEIFA (socio-Economic Index for areas), and diagnosis period. Abbreviations: ALL: acute lymphoid leukemia; AML: acute myeloid leukemia.

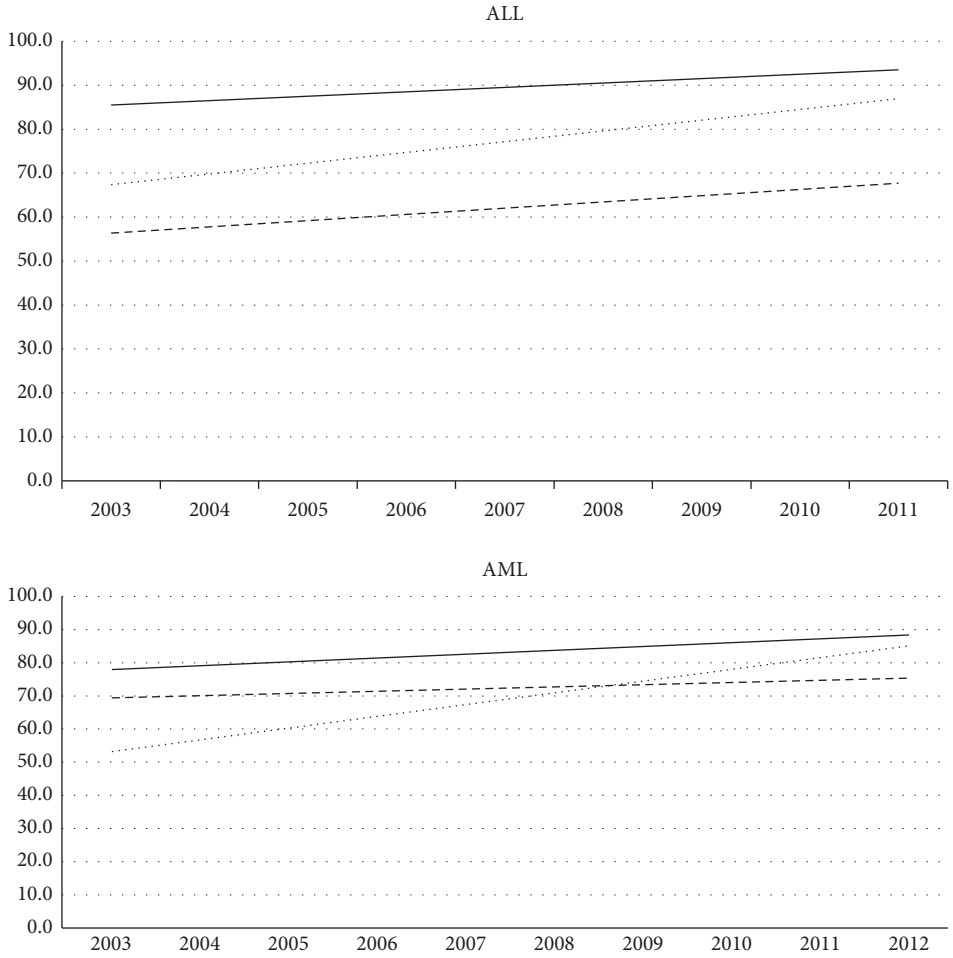

Figure 1: Temporal trend of 5-yearcancer-specific survival (%) for ALL and AML in 2003–2015 in NSW. ____ children ages 0–14; . . .. . . AYAs ages 15–24; - - - older adults ages 25–39; *X* axis: diagnosis year; *Y* axis: probability of 5-year cancer specific survival.

3 days. For AML, the 5-year survival was 77.7% and 74.4%, respectively. The start of initial treatment was not associated with survival from ALL and AML, after adjusted for age, sex, country of birth, residential remoteness, SEIFA, and diagnosis period. However, initial combined modality plus treatment was associated with higher AML mortality, with the aSHR (95% CI) being 2.34 (1.27–4.32).

The risk of ALL or AML mortality was more than doubled in patients lacking recorded treatment within 12 months after diagnosis (aSHR 2.48, 95% CI 1.01–6.10 for ALL and aSHR 2.85, 95% CI 1.80–4.54 for AML).

Among those having treatment within 12 months, combined modality treatment was associated with a higher risk of mortality of 69% (aSHR 1.69, 95% CI 1.13–2.53) for ALL and 111% (aSHR 2.11, 95% CI 1.45–3.07) for AML, comparing with chemotherapy only.

The association of treatment with ALL mortality differed by age group. Specifically, having combined modality treatment was associated with increased mortality in children (aSHR 2.67, 95% CI 1.53–4.67), but not for AYAs (aSHR 1.26, 95% CI 0.67–2.47) nor adults (aSHR 1.26, 95% CI 0.60–2.67; interaction $p = 0.017$) (Supplementary Table).

4. Discussion

We used linked population-wide cancer registry and health-services data to investigate treatment and survival for people with ALL and AML in NSW for ages 0–14, 15–24, and 25–39 years in 2003–2015.

The present data show that overall, the 5-year disease-specific survival for ALL increased from 83% for 2003–2007 diagnoses to 88% for 2008–2012, and correspondingly from 71% to 74% for AML in people aged 0–39 years. For AYAs, the survival increased more steeply from 72% to 83% for ALL and 60% to 79% for AML. The survival experienced by AYAs was comparable to that indicated by Australian national relative survival estimates of 79% for ALL and 77% for AML in 2010–2014 [2]. These are high survival figures by world standards [33], with the AML survival being higher than for the USA (56%) in 2003–2010 [34] and the UK for 2006 (53%) [35].

Despite survival gains, the data indicated that AYA and adults had a higher mortality risk than children. The upward gradient in risk of mortality with increasing age appeared to be the most pronounced for ALL. The lack of recorded

Table 4: 5-year survival (%) and the relative risk of mortality (SHR (95% CI)) associated with treatment in patients aged 0–39 years with acute leukemia in NSW, 2003–2015.

	ALL			AML		
	5-year survival[a]	Unadjusted SHR[b]	Adjusted SHR[b]	5-year survival[a]	Unadjusted SHR[b]	Adjusted SHR[b]
Initial treatment start following diagnosis						
Within 3 days	85.6	1.00	1.00	77.7	1.00	1.00
>3 days	82.0	1.40 (1.01–1.93)	0.92 (0.65–1.31)	74.4	1.15 (0.78–1.68)	1.14 (0.76–1.74)
Initial treatment type						
Chemotherapy only	84.2	1.00	1.00	77.0	1.00	1.00
Chemotherapy + other treats	75.0	1.61 (0.18–14.10)	0.58 (0.06–5.49)	54.3	2.10 (1.18–3.73)	2.34 (1.27–4.32)
Having treatment within 12 months after diagnosis						
Yes	84.3	1.00	1.00	76.0	1.00	1.00
No	62.1	3.20 (1.52–6.73)	2.48 (1.01–6.10)	53.9	2.53 (1.68–3.82)	2.85 (1.80–4.54)
Treatment type within 12 months following diagnosis						
Chemotherapy only	87.5	1.00	1.00	82.0	1.00	1.00
Chemotherapy + other treats	71.0	2.58 (1.84–3.59)	1.69 (1.13–2.53)	66.2	2.05 (1.42–2.96)	2.11(1.45–3.07)

[a]% of 5-year leukemia survival from Kaplan-Meier product-limit disease-specific estimates; date of censoring of live cases - Dec 31, 2015. [b]Sub-hazard ratio (SHR) for leukemia mortality from competing risk regression analysis using death of other causes other than leukemia as competing risk; adjusted SHR from multivariate competing risk regression adjusted for age, sex, country of birth, residential remoteness, SEIFA quintile, diagnosis period. Abbreviation: ALL-acute lymphoid leukemia; AML-acute myeloid leukemia. ALL and AML based on SEER AYA site recode employed in Australia.

treatment and use of combined treatment modalities in these two age groups were associated with poorer outcomes. We found that having multiple treatment types was associated with a higher mortality for both ALL and AML, especially for children with ALL. Further research is needed to determine the most effective chemotherapy protocols for treating leukemias with different cytogenic characteristics and biomarkers. Also, there is substantial ongoing research worldwide to identify risk groups more accurately in leukemia based on recently developed molecular and genomic analyses [36] with appropriate tailored therapy as well as a degree of personalized medicine [37].

It has been reported that treatment for AYA patients with childhood ALL protocols rather than adult-derived regimens was associated with better outcomes [38]. We lacked the range of data in this study to fully investigate this aspect. Our data did confirm, however, that AYAs treated in a paediatric cancer centre tended to have an earlier treatment start than those treated in adult centres, which is consistent with the findings reported by the Australian Youth Cancer Service [15].

The delay in starting leukemia treatment in AYA and adults could be multifactorial: including the unavailability of data of the first therapy given as an inpatient at the time of diagnosis, commencing with radiotherapy, seeking MDT consultation and direction, delays due to the presence of other disease complications, or logistical issues; in addition, potentially data on treatments with new therapies in ambulatory settings may not have been recorded in our data sources if they were yet to be listed for health-insurance rebate. Despite these speculations, we did not find the initial treatment start was associated with the risk of mortality.

The reasons patients were not reported to have been treated within 12 months with chemotherapy could be 1. Treatment data not linked (e.g., 5% of cancer cases in the NSW cancer registry are not linked with NSW hospital inpatient data, as seen in this cohort (supplementary figure), potentially reflecting patient mobility; and 2. Patients residing in local health districts that border other states or territories could have their treatment provided in other states, where data retrieval would require the establishment of national big data infrastructure. The impact on outcomes of possible treatment interstate for people who live in local health districts that border other states or territories has been tested in the sensitivity analyses, which show no impact on outcome; it is possible, however, that some patients may seek medical treatment in birth countries or others due to cultural issues.

It is reassuring that survival did not differ by sex, country of birth, residential remoteness, or diagnosis period. However, initial treatment start was observed to be later for ALL patients residing in outer regional and remote areas, and for cases diagnosed in the most recent diagnostic period of 2013–2015. These observations warrant follow-up investigation, including a review of referral practices, to better understand these differences.

This study extends our earlier AYA research by investigating age differences in acute ALL and AML survival and treatment, using linked Registry and health-service data in NSW [4]. We have explored the extent to which age disparities in leukemia survival were related to treatment start times, initial treatments, and treatments in the 12 months following diagnosis.

The relatively long study period enabled the exploration of survival trends among age groups. The study population was large enough to compare the age differences separately by acute leukemia types and provided a whole-of-population view, which could not have been achieved without data linkage. We conducted sensitivity analyses by excluding people residing close to NSW borders whose data may have been missed through treatment in other jurisdictions. We also explored differences in outcomes by the country of birth classified using the Human Development Index (developing vs developed country).

Study limitations include the use of data routinely collected for other reasons that were not designed to address study aims and included gaps in biomarkers. While data linkage had the advantage of population-wide coverage and was technically straightforward, there were uncertainties in the reliability of exact dates of diagnosis and treatment starts. Nonetheless, equivalent coding procedures were followed by the Registry, irrespective of sociodemographic characteristic and cancer type. We, therefore, consider that relative differences in measures of times and other characteristics were likely to be reliable.

Another limitation was the lack of clinical detail for diagnostic and prognostic characteristics and staging, which are important for treatment planning (e.g., results of lumbar punctures and imaging, presence of cytogenic and biomarkers at diagnosis, and performance status). The biological variations among AYA with ALL are important considerations when developing optimal therapy to improve survival [39].

Also, treatment details available to us were limited to broad categorisations. Chemotherapy, surgery, and other treatment were often broadly classified; also, generic codes often complicated the distinction of cancer therapies as such from supportive care [18, 29]. Treatment provided interstate, overseas, or in trials that were not recorded in these routine data sources was missing which weakened the database.

Death outcomes were censored on December 31st, 2015, which limited followup duration for the more recently diagnosed cases for survival estimates. The lack of population-based data on family history, disease progress, patient-reported outcomes, psychosocial support, and fertility preservation was a limitation as these data are needed at the population level to better inform models of service delivery. Although some loss of accuracy may be anticipated with routinely collected data, we found data linkage to be technically straightforward and to facilitate "big picture" research that complements focused studies and trials and facilitates evidence-basedhealth-service administration.

5. Conclusions

Leukemia survival for ages 0–39 years increased during the 2003–2015 diagnostic period. AYAs and older adults had a higher risk of leukemia death than children, with this

difference being more pronounced for ALL than AML. Compared to AYAs, children were more likely to start treatment within three days following diagnosis and to be treated exclusively with chemotherapy. Having multiple treatment types was associated with a higher risk of mortality, which may reflect recourse to the use of broader treatment approaches for more severe diseases. Further investigation is also needed into more specific treatment regimens by leukemia subtype to explore age disparities more fully in treatment and survival outcomes.

Data Availability

Data analysed for this paper are not able to be shared on any publicly available repository due to NSW privacy laws. Researchers can use these data with research ethics committee and data custodian approvals.

Ethical Approval

Approval for this study was provided by the NSW Population Health Services Research Ethics Committee (Ref: 2015/05/585), the Australian Institute of Health and Welfare (AIHW) Ethics Committee (Ref: EO2016/1/224), and the Aboriginal Health and Medical Research Council (AH&MRC) of NSW Ethics Committee (Ref: 1201/16).

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Study concept was carried out by ML and DR. Study design was carried out by ML, DR, and DC. Data acquisition was carried out by DR and DC. Data analysis was carried out by ML. Data interpretation was carried out by ML and DR. Manuscript writing was carried out by ML. Review of the manuscript was carried out by ML, AA, LD, PKB, DR, and DC. All authors read and approved the final manuscript. All authors qualify for the authorship according to the journal criteria of authorship.

Acknowledgments

The authors would like to thank the Centre for Epidemiology and Evidence, NSW Ministry of Health, and the Cancer Institute NSW for the use of these data. The authors are grateful to Dr. George Zhao for his assistance with interpreting treatment codes. Open access publishing facilitated by University of South Australia, as part of the Wiley - University of South Australia agreement via the Council of Australian University Librarians.

Supplementary Materials

Supplementary Figure. Population flow chart of Acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML) cases in NSW Cancer Registry 2003–2015 linked with treatment records. Supplementary Table: SHR (95% CI) a of ALL mortality associated with treatment type varied among age groups (p for interaction = 0.017) in NSW, 2003–2015. (*Supplementary Materials*)

References

[1] Leukemia Foundation, "Leukemias," 2021, https://www.leukaemia.org.au/blood-cancer-information/types-of-blood-cancer/leukaemia/.

[2] Australian Institute of Health and Welfare, *Cancer in Adolescents and Young Adults in Australia*, AIHW, Canberra, Australia, 2018.

[3] L. M. Force, I. Abdollahpour, S. M. Advani et al., "The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017," *The Lancet Oncology*, vol. 20, no. 9, pp. 1211–1225, 2019.

[4] M. Li, A. Anazodo, L. Dallapozza, P. K. Baeza, D. Roder, and D. Currow, "Cancer profiles, times to treatment, and survival for adolescents and young adults: comparisons with children and older adults in New South Wales, Australia," *Journal of Adolescent and Young Adult Oncology*, vol. 11, no. 5, pp. 443–450, 2022.

[5] M. Belson, B. Kingsley, and A. Holmes, "Risk factors for acute leukemia in children: a review," *Environmental Health Perspectives*, vol. 115, no. 1, pp. 138–145, 2007.

[6] Y. Guo, W. Wang, and H. Sun, "A systematic review and meta-analysis on the risk factors of acute myeloid leukemia," *Translational Cancer Research*, vol. 11, no. 4, pp. 796–804, 2022.

[7] F. M. Onyije, A. Olsson, D. Baaken et al., "Environmental risk factors for childhood acute lymphoblastic leukemia: an umbrella review," *Cancers*, vol. 14, no. 2, p. 382, 2022.

[8] Australian Institute of Health and Welfare, *Cancer in Australia 2019. Cancer Series No. 119*, AIHW, Canberra, Australia, 2019.

[9] C. H. Pui and W. E. Evans, "A 50-year journey to cure childhood acute lymphoblastic leukemia," *Seminars in Hematology*, vol. 50, no. 3, pp. 185–196, 2013.

[10] Leukemia Foundation, "Childhood ALL treatment," 2021, https://www.leukaemia.org.au/blood-cancer-information/types-of-blood-cancer/childhood-blood-cancers/childhood-all/treatment/.

[11] Leukemia Foundation, "National strategic action plan for blood cancer," 2020, https://www.leukaemia.org.au/national-action-plan/.

[12] Cancer Institute New South Wales, "Acute lymphoblastic leukaemia ALL06 treatment overview INTERIM," 2021, https://www.eviq.org.au/haematology-and-bmt/leukaemias/acute-lymphoblastic-leukaemia/3825-acute-lymphoblastic-leukaemia-all06-treatment.

[13] F. Carobolante, S. Chiaretti, C. Skert, and R. Bassan, "Practical guidance for the management of acute lymphoblastic leukemia in the adolescent and young adult population," *Therapeutic Advances in Hematology*, vol. 11, pp. 1–25, 2020.

[14] Leukemia Foundation, "Supportive care," 2019, https://www.leukaemia.org.au/blood-cancer-information/the-blood-cancer-journey/in-active-treatment/blood-cancer-treatment-options/supportive-care/.

[15] P. Patterson, K. R. Allison, H. Bibby et al., "The Australian Youth cancer service: developing and monitoring the activity of nationally coordinated adolescent and young adult cancer care," *Cancers*, vol. 13, no. 11, p. 2675, 2021.

[16] National Cancer Institute, *Surveillance, Epidemiology, and End Results Program*, National Cancer Institute, Bethesda, Maryland, 2019.
[17] D. W. S. Esteban, A. Laudico, and D. Parkin, "Manual for cancer registry personnel," *IARC Technical Report No 10 Lyon (FRA)*, International Agency for Research on Cancer, 1995.
[18] Australian Government and Department of Health, "MBS online," 2020, https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home.
[19] Australian Government and Department of Health, "About the PBS," 2020, https://www.pbs.gov.au/info/about-the-pbs.
[20] The Sax Institute, "Secure unified research environment," 2020, https://www.saxinstitute.org.au/our-work/sure/.
[21] M. Li, L. Holliday, D. Roder et al., "Degree of cancer spread at presentation and survival among adolescents and young adults in New South Wales, Australia," *Journal of Adolescent and Young Adult Oncology*, vol. 10, no. 2, pp. 156–163, 2021.
[22] E. K. T. Tracey, A. Dobrovic, and D. Currow, *Cancer in NSW: Incidence and Mortality Report 2008*, Cancer Institute NSW, Sydney, Australia, 2010.
[23] World Health Organization, *International Classification of Diseases for Oncology*, WHO, Geneva, Australia, 2000.
[24] Australian Bureau of Statistics (ABS), *Remoteness Structure*, ABS, Canberra, Australia, 2014.
[25] Australian Bureau of Statistics (ABS), *Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA)*, ABS, Canberra, Australia, 2013.
[26] D. C. Currow, H. You, S. Aranda et al., "What factors are predictive of surgical resection and survival from localised non-small cell lung cancer?" *Medical Journal of Australia*, vol. 201, no. 8, pp. 475–480, 2014.
[27] Cancer Council Victoria and Department of Health Victoria, *Optimal Care Pathway for People with Acute Myeloid Leukemia*, Cancer Council Victoria, Melbourne, 2021.
[28] V. W. Chen, C. R. Eheman, C. J. Johnson et al., "Enhancing cancer registry data for comparative effectiveness research (CER) project: overview and methodology," *J Registry Manag*, vol. 41, no. 3, pp. 103–112, 2014.
[29] National Centre for Classification in Health, *Australian Classification of Health Interventions (ACHI)*, NSW, Australia, 2010.
[30] P. Armitage and G. Berry, *Statistical Methods in Medical Research*, Blackwell Scientific Publications, Hoboken, NJ, USA, 1987.
[31] P. C. Austin and J. P. Fine, "Practical recommendations for reporting Fine-Gray model analyses for competing risk data," *Statistics in Medicine*, vol. 36, no. 27, pp. 4391–4400, 2017.
[32] StataCorp, *STATA Data Analysis and Statistical Software*, StataCorp LP, College Station, Texas, 2016.
[33] A. Bonaventure, R. Harewood, C. A. Stiller et al., "Worldwide comparison of survival from childhood leukaemia for 1995–2009, by subtype, age, and sex (CONCORD-2): a population-based study of individual data for 89 828 children from 198 registries in 53 countries," *The Lancet Haematology*, vol. 4, no. 5, pp. e202–e217, 2017.
[34] National Cancer Institute, *Surveillance, Epidemiology, and End Results Program*, SEER Cancer Statistics Review 1975–2011, 2014, https://seer.cancer.gov/archive/csr/1975_2011/results_single/sect_28_table.03.pdf.
[35] A. Shah, T. M. Andersson, B. Rachet, M. Björkholm, and P. C. Lambert, "Survival and cure of acute myeloid leukaemia in England, 1971-2006: a population-based study," *British Journal of Haematology*, vol. 162, no. 4, pp. 509–516, 2013.
[36] E. J. Duncavage, M. C. Schroeder, M. O'Laughlin et al., "Genome sequencing as an alternative to cytogenetic analysis in myeloid cancers," *New England Journal of Medicine*, vol. 384, no. 10, pp. 924–935, 2021.
[37] A. Collignon, M. A. Hospital, C. Montersino et al., "A chemogenomic approach to identify personalized therapy for patients with relapse or refractory acute myeloid leukemia: results of a prospective feasibility study," *Blood Cancer Journal*, vol. 10, no. 6, p. 64, 2020.
[38] L. S. Muffly, N. Reizine, and W. Stock, "Management of acute lymphoblastic leukemia in young adults," *Clinical Advances in Hematology and Oncology*, vol. 16, no. 2, pp. 138–146, 2018.
[39] J. W. Lee, "Optimal therapy for adolescents and young adults with acute lymphoblastic leukemia-current perspectives," *Blood Res*, vol. 55, no. S1, pp. S27–S31, 2020.