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Acute lymphoblastic leukemia: A population-based study of outcome in the United States based on the surveillance, epidemiology, and end results (SEER) database, 1980–2017

Koji Sasaki¹, Elias Jabbour¹, Nicholas J. Short¹, Nitin Jain¹, Farhad Ravandi¹, Ching-Hon Pui², Hagop Kantarjian¹

¹Department of Leukemia, U.T. M.D. Anderson Cancer Center, Houston, Texas

²Departments of Oncology and Pathology, St. Jude Children’s Research Hospital, Memphis, Tennessee

Abstract

The treatment in acute lymphoblastic Leukemia (ALL) has evolved and improved dramatically over the past four decades. We assessed the outcome of ALL overall, and the two major subsets of Philadelphia chromosome (Ph)-positive and Ph-negative ALL by age, time periods, ethnicity, median household income, and geographic county area. A total of 12 788 patients diagnosed with ALL from 1980 to 2017 were included. We performed an analysis to better evaluate the outcome evolution in ALL according to time period and patient’s demographic factors. The overall 5-year survival rates have improved significantly over time, from 51% before 1990 to 72% since 2010. The survival rates for children (age 0 to 14 years) and adolescents (age 15 to 19 years) have improved from 73% and 55% before 1990 to 93% and 74% since 2010, respectively. Similarly, the rates had improved from 33% to 59% for adults 20 to 29 years old, 24% to 59% for 30 to 39 years old, and 14% to 43% for 40 to 59 years old between the two time periods. The rates remained under 30% in older patients (60+ years). Since 2010, patients with Ph-negative ALL had 5-year survival rate of 73% and those with Ph-positive ALL 50%. African Americans, Hispanic ethnicity, and lower household income were associated with inferior survival. The outcome of patients with ALL showed continued improvement across all age groups in the US. The recent introduction of targeted therapies, together with optimized supportive care, will continue to improve outcomes, particularly in older patients.

1 | INTRODUCTION

Acute lymphoblastic leukemia (ALL) accounts for about 10% of leukemias in the United States. About 6000 new cases of ALL are diagnosed each year.¹ The conventional treatment of ALL consists of multiple chemotherapeutic agents used in sequences of induction, consolidation, and maintenance over 2.5 to 3 years, with central nervous system (CNS)

Correspondence Koji Sasaki, Department of Leukemia, MD, Anderson Cancer Center, Houston, TX 77030. ksasaki1@mdanderson.org.

Koji Sasaki and Elias Jabbour contributed equally.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

prophylaxis, and the use of allogeneic stem cell transplantation (ASCT) in first or later remissions.² Recently, such intensive chemotherapy regimens, patterned after the original curative pediatric regimens, have resulted in cure rates of 80+% in childhood ALL, 40–50% in adult ALL, and less than 15% in older ALL.^{3–5}

Since 2000, the treatment of adult and older ALL (age 60+ years) has undergone rapid positive changes. These have included: (1) the addition of imatinib, and, later, more potent BCR-ABL1 tyrosine kinase inhibitors, to chemotherapy in Philadelphia chromosome (Ph)-positive and certain subtypes of Ph-like ALL^{3,6–10}; (2) the incorporation of CD20-directed antibodies (rituximab, ofatumumab) into the treatment of Burkitt disease and CD20-positive B-ALL^{11–14}; (3) the development of bispecific antibody constructs, antibody drug conjugates, and chimeric-antigen receptor (CAR) T-cell therapies targeting CD19 and CD22^{15–18}; and (4) the risk stratification by measurable residual disease.^{19–23}

Older patients with ALL have not benefited as much as younger patients from the intensive chemotherapy-based regimens due to the inherently more resistant disease features, comorbidities, and the poor tolerance of intensive chemotherapy (treatment interruptions, mortality in complete remission), as well as less transition to ASCT.^{24–27} In these patients, the historical cure rates are 10% or less.

Previous studies analyzed SEER data in specific subsets of patients with ALL.^{27–29} In this study, we analyzed the SEER data from 1980 until 2017 across all patient populations in order to quantify the improvement in ALL outcomes over the past four decades. We also evaluated the outcome evolution separately in Ph-positive and Ph-negative ALL, coded into the SEER data since 2010. Finally, we explored whether the outcome was associated with financial status, geography, or ethnicity.

2 | PATIENTS AND METHODS

2.1 | Patient database

The data from the SEER registries covering about 35% of the US population were used to identify patients diagnosed with ALL from 1980 until 2017. The SEER data originally included the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii, as well as the metropolitan areas of Detroit and San Francisco-Oakland. This later expanded to include Alaska, Arizona, California (San Jose-Monterey, Greater California), Georgia, Idaho, Kentucky, Louisiana, Massachusetts, New Jersey, New York, Washington (Seattle-Puget Sound), and Wisconsin.

We used the third edition of the International Classification of Disease for Oncology histology codes 9811/3, 9812/3, 9813/3, 9814/3, 9815/3, 9816/3, 9817/3, 9818/3, 9826/3, 9835/3, and 9836/3 to identify all patients with diagnostic codes: “B lymphoblastic leukemia/lymphoma, NOS,” “B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL1,” “B lymphoblastic leukemia/lymphoma with t(v;11q23); MLL rearranged,” “B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22);TEL-AML1,” “B lymphoblastic leukemia/lymphoma with hyperdiploidy,” “B lymphoblastic leukemia/lymphoma with hypodiploidy,” “B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32); IL3-IGH,”

“B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); E2A PBX1,” “Burkitt cell leukemia,” “Precursor cell lymphoblastic leukemia, NOS,” and “Precursor B-cell lymphoblastic leukemia,” respectively.

A total of 14 165 patients were identified in the SEER database.³⁰ We excluded 202 patients with adult T-cell leukemia/lymphoma, 489 patients who were reported by autopsy or death certificates without follow-up, and 686 patients with ALL and prior history of malignancy. The remaining 12 788 patients with de novo ALL were included in this analysis: 9727 before 2010, and 3061 since 2010. Ph-positive ALL was coded (code 9812/3) separately into the SEER data since 2010 (Supplemental Figure S1). A total of 549 coded patients with Ph-positive ALL were identified.

Since the Ph-positive code was available only since 2010, we analyzed the outcome of patients by time period and age group overall from 1980 until 2017. We then analyzed separately the outcomes of Ph-positive and Ph-negative ALL in the period of 2010–2017.

2.2 | Data analysis

The pre-treatment characteristics of patients were summarized using descriptive statistics. Categorical variables were compared using the chi-square test. To evaluate the outcome by age at diagnosis, patients were grouped by age 0–14, 15–19, 20–29, 30–39, 40–59, 60–69, and 70+ years. The age group cutoffs were selected by clinical relevance including pediatric, adolescence, young adult, middle age, older patients with potential candidates for intensive therapy and allogeneic stem cell transplant, and older patients who were not typically suitable for intensive therapy. We summarized the ethnicity of Asian or Pacific Islanders, American Indian/Alaska Native, and Unknown as Others. To evaluate the outcome by annual median household income at the county levels, patients were grouped by annual household income levels <\$50 000, \$50 000–\$75 000, and >\$75 000.^{31,32} The overall survival was calculated from the time of diagnosis to the time of death from any cause or last follow-up, whichever comes first.³³ We analyzed the overall survival using the Kaplan–Meier method with the log-rank test.^{34,35} We performed subgroup analysis by the presence of Ph status. We assessed 4- and 8-week mortality in each age group. To evaluate the number and percentage of cause of death at 3-month periods, histograms and stacked proportional histograms were assessed between 2000 and 2017 overall and by every 5-year period. Multiple imputations were performed for missing covariates using age at diagnosis, gender, ethnicity, diagnostic year, and geographic county areas. Poor financial status was defined as median annual household income less than \$50 000/year. The geographic county areas were divided by the 2013 Rural–Urban Continuum Codes, which distinguished metropolitan counties by the population size of their metro area, and nonmetropolitan counties by degree of urbanization and adjacency to a metro area. Univariate and multivariate Cox proportional regression analyses were performed to identify prognostic factors for survival. In the univariate and multivariate models, covariates included age at diagnosis, gender, diagnostic year, type of ALL, median household income, ethnicity, and geographic areas. SEER*Stat 8.3.6.1 statistical software, SPSS 24.0 software (IBM), and R 3.6.3 software (R Development Core Team) were used for data analyses.

3 | RESULTS

3.1 | Patients characteristics

Among the 12 788 patients evaluated, 5591 (44%) were females (Table 1). The median age was 11 years (range 0 to 85 + years); 13% of patients were aged 60 years or older. In patients with Ph-positive ALL in the 2010–2017 cohort, 33% were 60 years or older. Overall, 81% of patients were white and 65% were non-Hispanic white. The annual median household income was available in 77% of patients, including 878 (8%), 4792 (54%), and 4240 (38%) with an annual median income of <\$50 000, \$50 000–75 000, >\$75 000, respectively (Supplemental Table S1). Forty-four percent of patients lived in metropolitan areas with a population of more than one million people.

3.2 | Overall outcomes

The 5-year overall survival rate for the total population by treatment decade was 51% in 1980–1989, 61% in 1990–1999, 67% in 2000–2009, and 72% in 2010–2017 ($p < .001$) (Figure 1(A)). Figure 1(B) shows the estimated 5-year survival rates in the seven different age groups. The estimated 5-year survival rate was 85% in patients 0–14 years old, 61% in patients 15–19 years old, 44% in patients 20–29 years old, 40% in patients 30–39 years old, 28% in patients 40–59 years old, 19% in patients 60–69 years old, and 6% in patients 70 years and older ($p < .001$).

3.3 | Outcomes by time period and age

Next we analyzed the outcomes by time period and age (Table 2; Figures 2(A)–(G)). Across all age groups, the estimated 5-year survival rates continued to improve, highlighting the continued beneficial progress in ALL therapy across all age groups. By contrast, the 5-year survival rates for patients 70 years and older have made no progress, with the possible exception of the recent decade (2010–2017) when they appeared to have a small gain in survival.

With the introduction of tyrosine kinase inhibitors (TKIs), Ph-positive ALL was considered a separate ALL entity as of 2010. We then assessed the outcomes in Ph-positive and Ph-negative ALL in the time period of 2010–2017. The 5-year overall survival rates were 72% overall, 73% for the 2864 patients with Ph-negative ALL, and 50% for the 197 patients with Ph-positive ALL ($p < .001$; Figure 3). The estimated 5-year survival rates were 94% ($N = 16$), 83% ($N = 8$), 38% ($N = 14$), 58% ($N = 35$), 44% ($N = 59$), 32% ($N = 44$), and not available in patients with Ph-positive ALL between 0 and 14 years old, 15 and 19 years old, 20 and 29 years old, 30 and 39 years old, 40 and 59 years old, 60 and 69 years old, and 70 years and older, respectively ($p < .001$; Supplemental Table S2 and Supplemental Figure S2). In patients with Ph-negative ALL, the 5-year survival rates were 93%, 73%, 59%, 59%, 42%, and 28%, respectively ($p < .001$; Supplemental Figure S3). The 5-year survival rate for patients 70 years and older was 11%. Since the incidence of Ph-positive ALL increases with age, by performing age-matched comparison older patients with Ph-positive ALL had better outcome due to the availability of TKIs (Supplemental Figure S2F and G).

3.4 | Four-week and eight-week mortality

The 4- and 8-week mortality rates continued to improve over the four time periods. The 4-week mortality decreased from 10% in 1980–1989 to 5% in 2010–2017 (Supplemental Tables S3–S5). The 4- and 8-week mortality rates increased with age. Overall, these rates were 5% and 7% (5% and 9% in Ph-positive ALL) between 2010 and 2017. Of note, among patients 60 to 69 years old, the 4-week mortality was 27% in 1980–1989 and decreased to 13% in 2010–2017. Among patients 70 years and older, the 4-week mortality was 51% in 1980–1989, decreased, but remained at 37%, in 2010–2017.

3.5 | Cause of death

We then assessed the cause of death in patients with ALL between 2000 and 2017 overall and by every 5-year period. As expected, the most common cause of death was due to leukemia (77%, Supplemental Figure S4). The rate of death from ALL decreased with every 5-year period from 81% during the first 5-year period to 26% during the third 5-year period. In contrast, the proportion of death from second malignancies and cardiovascular diseases increased from 8% and 2% during the first 5-year period to 25% and 12% during the third 5-year period, respectively ($p < .001$; Supplemental Figure S4). Thus, among patients who survived for 10 years since the diagnosis, second malignancies and late relapse were the most common causes of death (26% and 25%, respectively), followed by cardiovascular diseases (12%).

3.6 | Socioeconomic evaluations

We evaluated the effect of financial status, ethnicity, and population density, but only since 2000, to highlight their effects in the recent (and more relevant) time period 2000–2017 and to minimize the effect of inflation over decades. The associations between financial status and race with outcomes are shown in Supplemental Figures S4A and B. Poorer financial status (median household income less than \$50 000/year) correlated with worse outcome overall (Supplemental Figure S5A). Outcome was also different by ethnicity, which is interrelated with financial status (Supplemental Figure S5B). Hispanic whites were significantly underrepresented in the older age group. Among non-Hispanic whites, 6% were 70 years or older, versus 2% among Hispanics ($p < .001$) (average life span 81.8 years among Hispanics and 78.6 years among non-Hispanic whites). Among ethnicity groups, Hispanic whites and Blacks had a tendency of worse survival (Supplemental Figure S5B). Blacks and Hispanic whites remained independent adverse prognostic factors in multivariate analysis (Supplemental Table S6). Finally, patients living in a small metropolitan area (population density $< 250\,000$) had a tendency of worse outcome, with a 5-year survival rate of 62% compared to 72% in the metropolitan areas above 1 million ($p = .013$ by univariate Cox regression; $p = .088$ by log-rank) (Supplemental Figure S5C); by multivariate analysis, lower population density was adverse independent prognostic factor for survival (Supplemental Table S6).

The multivariate analysis for survival confirmed that the early time period, older age at diagnosis, Hispanic or Black, lower median annual income, lower population density, and male gender were independent adverse prognostic factors for survival (Supplemental Table

S6). In patients aged 15 years and older, gender was not a prognostic factor for survival by univariate analysis ($p = .993$; HR, 1.000; 95% CI, 0.938–1.067).

4 | DISCUSSION

The SEER data in ALL from 1980 to 2017 highlights multiple important points.

The most important finding is that survival has improved significantly over time, especially for adults since 2000. The estimated 5-year survival rate improved from 51% before 1990 to 72% since 2010 (Figure 1(A)). Still, age is highly correlated with outcome regardless of the time period. The estimated survival rates for children (age 0 to 14 years) and adolescents (15 to 19 years) had improved from 73% and 55% before 1990 to 93% and 74% since 2010, respectively. The rates had also improved from 33% to 59% for adults 20 to 29 years old, 24% to 59% for adults 30 to 39 years old, and 14% to 43% for those 40 to 49 years old between the same time periods. Although the 5-year survival rates remained under 30% in older ALL (age 60+ years), a small gain had occurred since 2010, from 22% to 29% for patients between 60 and 69 years old and 7% to 13% for those aged 70+. Recently, the incorporation of inotuzumab and blinatumomab to lower-intensity chemotherapy over a 12–18-month treatment period resulted in a high rate of complete response (90 + %) and an estimated 5-year survival rate of 50 + % for adults with ALL.^{36,37} Among 727 older patients (aged >65 years) with ALL treated through the Medicare health insurance program, Li and colleagues¹⁴ reported a median overall survival of 10 months (95% CI, 8.3–12.7).²⁶ Given most older patients with ALL historically did not receive any therapy, the combination of targeted therapy with low-intensity therapy offers the opportunity for more tolerable and effective therapy in older patients.^{26,38}

A second important observation is that modifications of the dose-schedules of chemotherapy and in supportive care measures in both children and adults continued to improve outcomes in each age group over the four time periods. Since 2000, the outcomes improved in adult ALL, with a shift from regimens that mimicked adult AML regimens (shorter maintenance, reliance on ASCT) to regimens that mimicked pediatric-inspired regimens (intensification of the non-myelosuppressive drugs like steroids and vincristine in pediatric-inspired ALL regimens that incorporate asparaginase, Hyper-CVAD regimen and its derivatives).^{11,39–41}

A third important observation is the remarkable improved outcome for adults since 2010, the time when Ph-positive ALL was separated from Ph-negative ALL. The introduction of BCR-ABL1 tyrosine kinase inhibitors to chemotherapy in Ph-positive ALL regimens started in 2000.^{6–9} The estimated 5-year survival rate in adult ALL of 50% in Ph-positive disease reflects the addition of first and second-generation TKIs.^{6,7} This improvement was markedly observed in older patients 60+ years (5-year OS rates of 20% and 33% in Ph-negative and in Ph-positive ALL, respectively) ($p = .015$). The addition of CD20 antibodies (rituximab, ofatumumab) to chemotherapy started in 2000, but was established as a standard of care in adult patients with ALL since 2017.^{11–14,42–44} The use of inotuzumab and blinatumomab in frontline chemotherapy regimen is too recent to influence the SEER data results.^{36,37,45} The estimated survival of 73% in Ph-negative ALL could soon be significantly improved with

the addition of CD20, CD19, and CD22 antibodies to the chemotherapy in adult (age 30–46 years)⁴⁵ and older ALL (age 60 + years).^{36,37}

In our analysis, we confirmed the independent associations of several factors affecting survival, including ethnicity (African American and Hispanic ethnicity associated with worse outcome). The poorer outcome among African Americans may be due to several factors, including a higher incidence of co-morbidities (hypertension, diabetes, cardiovascular problems, and obesity) and financial status. Hispanic patients have a higher prevalence of Ph-like ALL phenotype,⁴⁶ which is associated with poor outcome.^{29,46–48}

There are several limitations in our study. First, the SEER database does not include treatment data. Park and colleagues used the US National Cancer Institute's SEER database to assess survival among 1675 older adults (aged ≥ 60 years) with ALL in the USA between 1980 and 2011.²⁷ Median overall survival was 4 months (95% CI 3–5) and 3-year overall survival was 12.8% (95% CI 11.2–14.5). These data included patients who did not receive any chemotherapeutic agent. Therefore, although these outcomes reflect real-life practice, they are substantially influenced by patients who did not receive any anti-leukemic treatment. The recent approval of novel generation TKIs, antibody drug conjugates, and bispecific antibody constructs may not be fully reflected in the survival improvement in this study. It is possible that novel agents may further improve ALL outcomes with longer follow-up. Second, the assessment of the socioeconomic factors is limited to an evaluation closely interrelated with racial disparity. The broader inclusion of socioeconomic variables such as education levels, individual median income or household income with the adjustment of inflation over decades, and insurance status might better reflect the reasons for differences in outcome independent of ethnic status. The impact of ethnic disparities by multivariate analysis (other than Hispanic ethnicity, associated with Ph-like ALL) needs to be interpreted cautiously. Third, the coding data of Ph + status was not available before 2010. It is possible that patients with ALL received treatment with or without TKI therapy. However, we confirmed the survival improvement consistently in the total cohort over decades. Given the small number of patients with Ph-positive ALL, the results of outcome needs cautious interpretation.

In summary, the SEER data shows a continued improvement in patient outcomes over the four calendar periods and across all age categories, even in older ALL (age 70+ years) in the past decade. Ongoing trials incorporating the more potent BCR-ABL1 TKIs (ponatinib) into the Ph-positive ALL therapy, and more potent antibodies (inotuzumab, blinatumomab) into intensive and lower-intensity chemotherapy in Ph-negative ALL during induction consolidation and maintenance, will improve the ALL outcomes further across all age categories in the next decade in the real world.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The SEER Data is available after the request and subsequent approval at the SEER data repository.

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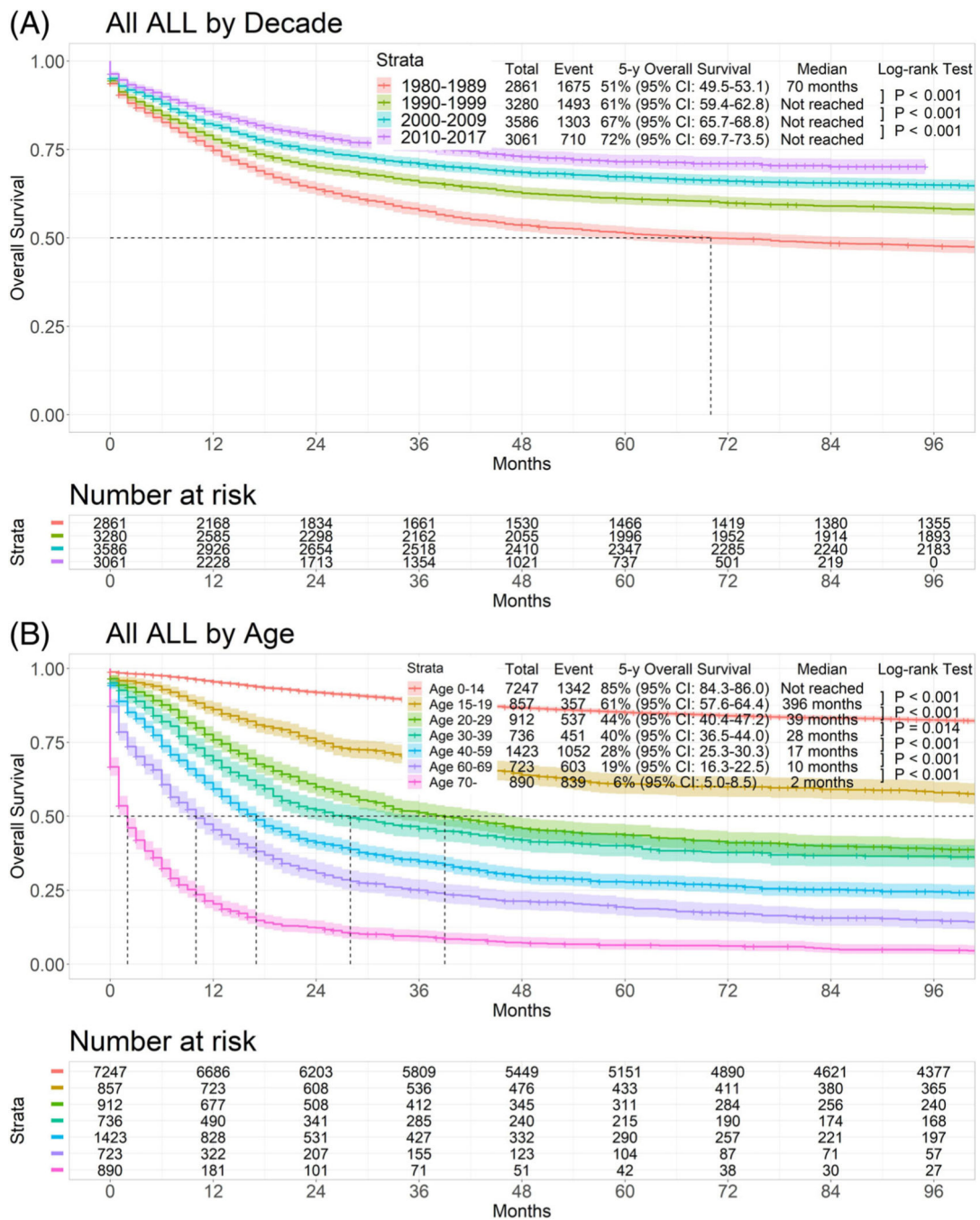


FIGURE 1.
Survival of all types of acute lymphoblastic leukemia by age and decade

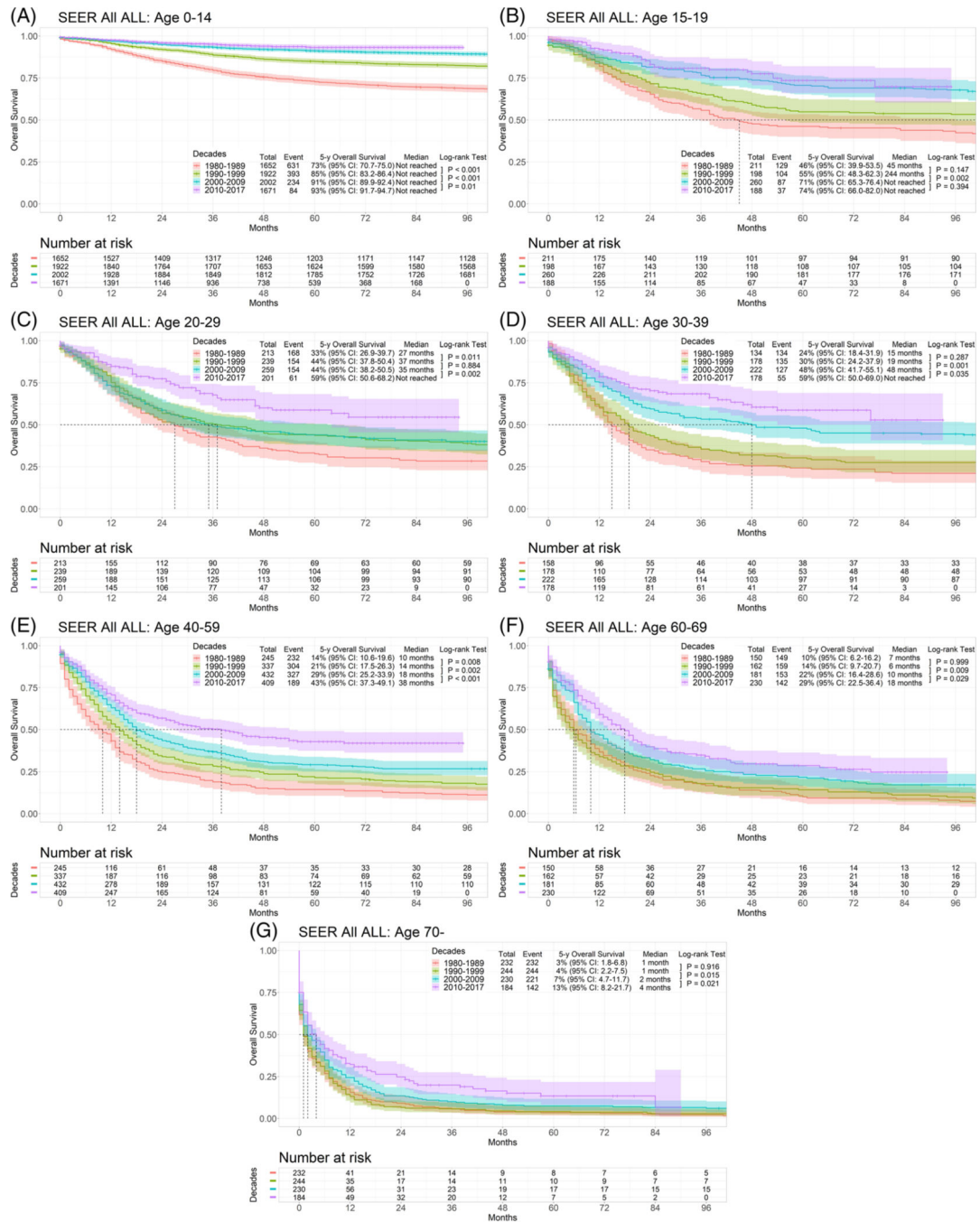


FIGURE 2. Survival of acute lymphoblastic leukemia by decade in each age group

SEER ALL: Philadelphia chromosome

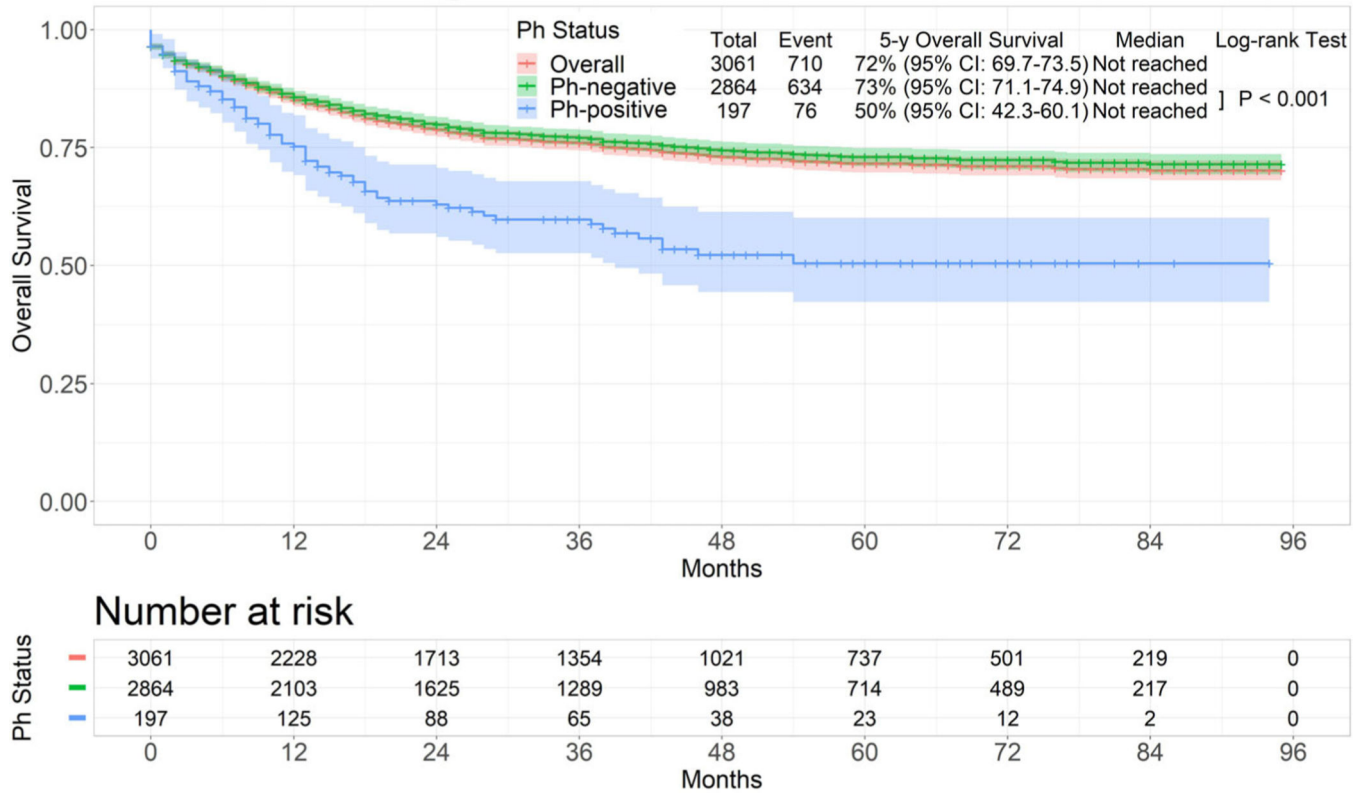


FIGURE 3. Survival of acute lymphoblastic leukemia by Philadelphia chromosome status

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TABLE 1

Patient characteristics

Variables	ALL subgroups			p
	ALL N = 12 788	ALL N = 12 591	Ph-positive ALL N = 197	
Age, No. (%)				
0–14 years	7247 (57)	7231 (57)	16(8)	<.001
15–19 years	857 (7)	849 (7)	8 (4)	
20–29 years	912 (7)	898 (7)	14 (7)	
30–39 years	736 (6)	701 (6)	35 (18)	
40–59 years	1423 (11)	1364 (11)	59 (30)	
60–69 years	723 (6)	679 (5)	44 (22)	
70–85+ years	890 (7)	869 (7)	21 (11)	
Sex, No. (%)				
Female	5591 (44)	5502 (44)	89 (45)	.678
Ethnicity, No. (%)				
Non-Hispanic white	8369 (65)	8249 (66)	120 (61)	.105
Hispanic white	1976 (16)	1950 (16)	26 (13)	
Black	935 (7)	916 (7)	19 (10)	
Other	1508 (12)	1476 (12)	32 (16)	
Diagnostic year, No. (%)				
1980–1989	2861 (23)	2861 (23)	0	<.001
1990–1999	3280 (26)	3280 (26)	0	
2000–2009	3586 (28)	3586 (29)	0	
2010–2017	3061 (24)	2864 (23)	197 (100) ^a	

Abbreviations: ALL, acute lymphoblastic leukemia; Ph, Philadelphia chromosome.

^aThe histologic code of Philadelphia chromosome-positive acute lymphoblastic leukemia were available since 2010.

Summary of 5-year and 10-year survival in patients with acute lymphoblastic leukemia by age and time period

TABLE 2

Variables	N	Estimated 5-year survival rate (%)				
		Overall	1980–1989	1990–1999	2000–2019	2010–2017
Age 0–14 years	7247	85	73	85	91	93
Age 15–19 years	857	61	46	55	71	74
Age 20–29 years	912	44	33	44	44	59
Age 30–39 years	736	40	24	30	48	59
Age 40–59 years	1423	28	14	21	29	43
Age 60–69 years	723	19	10	14	22	29
Age 70+ years	890	6	3	4	7	13
Variables	N	Estimated 10-year survival rate (%)				
		Overall	1980–1989	1990–1999	2000–2019	2010–2017
Age 0–14 years	7247	82	67	82	88	NA
Age 15–19 years	857	57	42	53	66	NA
Age 20–29 years	912	38	28	38	40	NA
Age 30–39 years	736	35	21	27	42	NA
Age 40–59 years	1423	23	11	17	25	NA
Age 60–69 years	723	13	7	9	15	NA
Age 70+ years	890	4	1	3	5	NA

Abbreviation: NA, not available.