Population-Level Outcomes of Pediatric Acute Promyelocytic Leukemia in the United States

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Objective To determine whether the population level outcomes of pediatric acute promyelocytic leukemia have improved over time.

Study design We conducted a retrospective analysis of the Surveillance Epidemiology and End Results database for patients with acute promyelocytic leukemia, up to 20 years of age, diagnosed between 1976 and 2016 and actively followed. Patients were stratified based on their period of diagnosis (1976-1989, 1990-1999, 2000-2009, 2010-2016) to assess the temporal trends in overall survival and early mortality.

Results A total of 553 patients with a median age of 15 years (range, 0-20 years) were included. The 5-year overall survival increased significantly over time (by 22.6% from 1976 to 1989; by 59.2% from 1990 to 1999; by 77.7% from 2000 to 2009; and by 88.9% from 2010 to 2016; $P < .001$). Early mortality showed an improvement over time in the most recent cohort (by 14% from 1976 to 1989; by 13.5% from1990 to 1999; by 13.3% 2000 to 2009; and by 7.2% from 2010 to 2016) after adjusting for other demographic characteristics in a logistic regression model. On multivariate analysis of overall survival, diagnosis in the earlier time periods was associated with higher mortality as compared with the 2010-2016 period. Age, sex, and race/ethnicity were not significant predictors of overall survival.

Conclusions Outcomes of pediatric acute promyelocytic leukemia have continued to improve over time at the population level. *(J Pediatr 2020;223:114-9)*.

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia and accounts for about 10% of pediatric acute myeloid leukemia cases. It is generally diagnosed at a median age of 12 years with female preponderance and higher frequency in Hispanics.[1-3] The disease is characterized by the chromosomal translocation t (15,17) and PML-RARA fusion with hematologic abnormalities such as hyperfibrinolysis and disseminated intravascular coagulation. In prior years, the management of pediatric APL with chemotherapies such as daunorubicin and cytarabine produced 75%-80% complete remission and 25%-40% cure rates.[2] Since the introduction of targeted agents such as all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), cure rates now exceed 90%.[4,5] However, the outcomes reported in clinical trials are derived from carefully selected patients and are often less reflective of the population-level outcomes. Although there are several studies in adults showing improving trends in the population level outcomes of APL over time, there is limited information in the pediatric population to demonstrate the same.[6,7]

Several major advances over time have been seen in APL such as the use of ATRA in frontline therapy, molecular monitoring with minimal residual disease assessment, effective salvage strategies, and better supportive care. In addition, there is more awareness about early death and late complications of APL. However, it is unclear if these advancements have improved the population-level outcomes of pediatric APL over time. In the current study, our objectives are to describe the trends in outcomes of pediatric APL over time in the US using the Surveillance Epidemiology and End Results (SEER) database.

Methods

We performed a retrospective analysis of pediatric APL using SEER database, a population-based registry maintained by the National Cancer Institute in the US. Patients were identified using the *International Classification of Diseases for Oncology* code (9866) for APL from the SEER-18 registry.[8] It included the following geographical areas: San Francisco-Oakland, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, Alaska Natives, Rural Georgia, California (excluding San Francisco-Oakland, San Jose-Monterey, and Los Angeles), Kentucky, Louisiana, New Jersey, and Greater

APL	Acute promyelocytic leukemia
ATO	Arsenic trioxide
ATRA	All-trans retinoic acid
SEER	Surveillance Epidemiology and End Results

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Georgia. Information about patient demographics and survival are available in the database. However, information on other aspects such as treatment drugs, relapse, stem cell transplantation, and other prognostic factors are not available. Information on insurance status was available only from 2007 and we did not have details about individual types of insurance.

Selection criteria included patients up to 20 years of age who were diagnosed with APL and under active follow-up. We extracted information about patient demographics, period of diagnosis, and duration of survival from the database. This research did not involve interaction with human subjects or the use of any personal identifying information and was exempted from the institutional review board approval. Informed consent was not applicable to this study.

Statistical Analyses

We used descriptive statistics for baseline characteristics. Period of diagnosis was arbitrarily divided into groups (1976-1989, 1990-1999, 2000-2009, and 2010-2016) to assess the temporal trend in improvement of outcomes in successive cohorts. To ensure that the outcomes did not start to differ in a particular year to justify using that as a cut-off, we performed a breakpoint analysis.[9] The presence of a potential breakpoint in the linear relationship between year of diagnosis and the outcomes of interest was evaluated by obtaining an estimate with standard error for each year within the appropriate regression model. The Davies test was used in a linear regression model of the estimates on year with inverse squared standard error as weights. The R package segmented v 0.5-3 was used for this analysis (The R Foundation, Vienna, Austria). No breakpoints were identified (**Table I**; available at www.jpeds.com).

Early Mortality

Early mortality was defined as death within the first month of follow-up. Logistic regression was used to evaluate the changes in probability of early death over the cohorts adjusting for patient sex, age, and race/ethnicity.

Survival

Overall survival was calculated from the time of diagnosis to death from any cause and patients were censored if they were alive at the last follow-up or at the end of the study. Overall survival was administratively truncated at 7 years and probabilities were computed using the Kaplan-Meier estimator. A log-rank test was used to compare the overall survival between groups. An exploratory analysis identified a high prevalence of early death and a differential effect of covariates on the hazard during the first month and the remaining follow-up. Hence, a detailed survival analysis was performed conditioning on not experiencing early death, starting with 1 month after the diagnosis. Cox proportional hazards regression was used to conduct a covariate-adjusted analysis of the effect of cohort on overall survival after 1 month. The proportional hazards assumption and the linearity of the effect of continuous predictors (age) was assessed graphically using plots of cumulative sums of martingale residuals. No deviations from the assumptions were found. A P value of less than .05 indicated statistical significance. Statistical analysis was performed using SEER*Stat Software and SAS version 9.2 (Cary, North Carolina).

Results

Baseline Characteristics

We identified 553 patients with APL who met the study criteria. The median age of the cohort was 15 years (range, 0-20 years). The majority of the patients were in the age group above 10 years (75.4%), females (52.1%), and non-Hispanic whites (42.9%). Hispanics constituted for 35.3% of the study cohort. Information on insurance status was available only from 2007. In this group, only 1.6% of patients were uninsured. **Table II** summarizes the cohort's baseline characteristics.

Survival

The median overall survival was not reached. The 5-year overall survival of the entire cohort was 72.7% (range, 68.6%-76.4%). When stratified by the period of diagnosis, the 5-year overall survival was significantly higher for patients diagnosed between 2010 and 2016 (88.9%) as compared with those diagnosed from 2000 to 2009 (77.7%), 1990 to 1999 (59.2%), and 1976-1989 (22.6%) ($P < .0001$) (**Figure 1**). When the analysis was restricted to patients who did not die within the first month of diagnosis (ie, those who did not have early mortality), the improvement in overall survival over time remained significant (5-year overall survival for 1976-1989 vs 1990 to 1999 vs 2000 to 2009 vs 2010 to 2016: 26.3% vs 68.4% vs 89.7% vs 95.7%, respectively; $P < .0001$) (**Figure 2**; available at www.jpeds.com). The 5-year overall survival did not vary significantly by factors such as age (age 0-5 years, 69.1%; age, 6-10 years 73.1%; age 11-15 years, 69.4%; age 16-20 years; 76.3%; $P = .62$; **Figure 3** [available at www.jpeds.com]), sex (males, 70.7%; females, 74.6%; $P = .27$; **Figure 4** [available at www.jpeds.com]) or race/ethnicity (Hispanic, 74%; non-Hispanic blacks, 64.6%; non-Hispanic whites, 72.4%; other non-Hispanics, 78.1%; $P = .42$; **Figure 5** [available at www.jpeds.com]).

Multivariate Analysis of Overall Survival

On multivariate analysis of overall survival after 1 month, diagnosis in the early period was associated with a higher risk of mortality as compared with those diagnosed from 2010 to 2016 (**Table III**). Age, sex, and race/ethnicity were not significant determinants of survival.

Early Mortality

Early mortality showed a significant improvement over time in the most recent cohort (14% from1976 to 1989; 13.5% from 1990 to 1999; 13.3% from 2000 to 2009; and 7.2%

Table II. Baseline characteristics

Variables	Cohort				
	Total (n = 553)	1976-1989 (n = 50)	1990-1999 (n = 74)	2000-2009 (n = 248)	2010-2016 (n = 181)
Age at diagnosis (y)					
Mean ± SD	13.5 ± 5.4	11.5 ± 6.0	13.6 ± 5.2	13.1 ± 5.4	14.7 ± 4.9
Median (min-max)	15.0 (0.0-20.0)	12.5 (0.0-20.0)	14.0 (1.0-20.0)	15.0 (1.0-20.0)	16.0 (0.0-20.0)
Missing	0	0	0	0	0
Age group (y)					
0-5	67 (12.1)	10 (20.0)	5 (6.8)	38 (15.3)	14 (7.7)
6-10	69 (12.5)	8 (16.0)	13 (17.6)	32 (12.9)	16 (8.8)
11-15	171 (30.9)	19 (38.0)	26 (35.1)	72 (29.0)	54 (29.8)
16-20	246 (44.5)	13 (26.0)	30 (40.5)	106 (42.7)	97 (53.6)
Missing	0	0	0	0	0
Sex					
Female	288 (52.1)	21 (42.0)	39 (52.7)	129 (52.0)	99 (54.7)
Male	265 (47.9)	29 (58.0)	35 (47.3)	119 (48.0)	82 (45.3)
Missing	0	0	0	0	0
Race/ethnicity					
Hispanic (all races)	195 (35.3)	5 (10.0)	26 (35.1)	100 (40.3)	64 (35.4)
Non-Hispanic black	62 (11.2)	5 (10.0)	3 (4.1)	31 (12.5)	23 (12.7)
Non-Hispanic white	237 (42.9)	37 (74.0)	33 (44.6)	92 (37.1)	75 (41.4)
Other non-Hispanic	59 (10.7)	3 (6.0)	12 (16.2)	25 (10.1)	19 (10.5)
Missing	0	0	0	0	0
Insurance					
Insured	231 (41.8)	0 (0.0)	0 (0.0)	65 (26.2)	166 (91.7)
Not collected (pre-2007)	303 (54.8)	50 (100.0)	74 (100.0)	179 (72.2)	0 (0.0)
Uninsured	9 (1.6)	0 (0.0)	0 (0.0)	2 (0.8)	7 (3.9)
Unknown	10 (1.8)	0 (0.0)	0 (0.0)	2 (0.8)	8 (4.4)
Missing	0	0	0	0	0

Values are number (column %) unless otherwise indicated.

from 2010 to 2016) after adjusting for age, sex, and race/ethnicity in a multivariate logistic regression model (Table IV). Early mortality was affected significantly by increasing age (Figure 6; available at www.jpeds.com). Sex and race/ethnicity were not statistically significant predictors of early mortality.

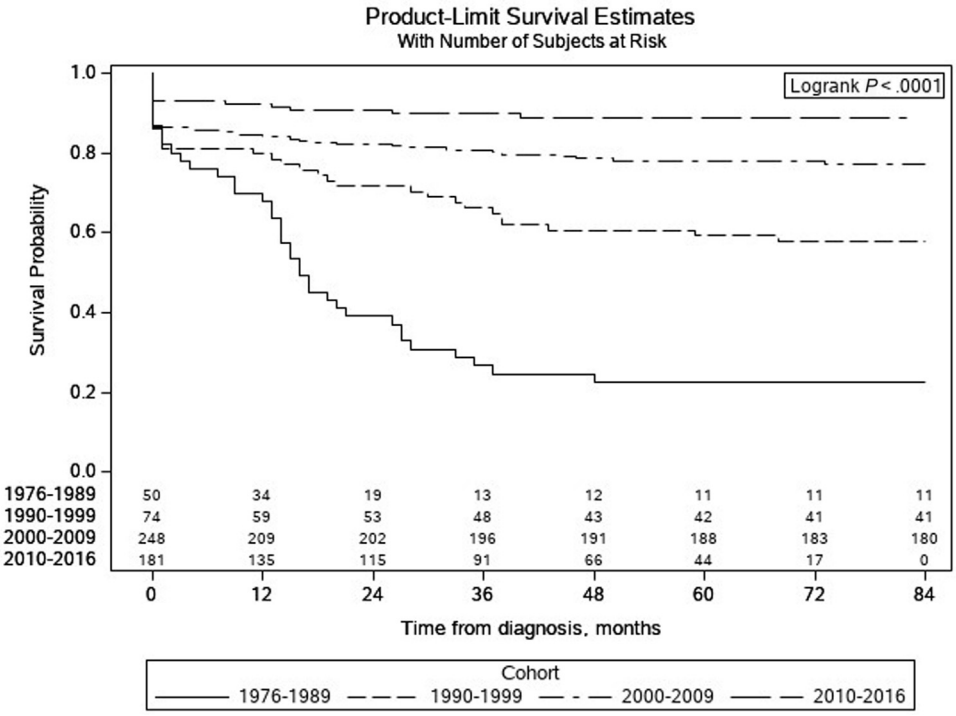

Figure 1. Overall survival by period of diagnosis.

Table III. Cox regression model of overall survival after 1 month (n = 490)

Description	Point estimate	Lower 95% Wald confidence limit	Upper 95% Wald confidence limit	*P* value
Cohort 1976-1989 vs 2010-2016	28.961	10.989	76.321	<.0001
Cohort 1990-1999 vs 2010-2016	8.530	3.193	22.788	<.0001
Cohort 2000-2009 vs 2010-2016	2.303	0.870	6.093	.0930
Sex: female vs male	0.856	0.544	1.348	.5021
Hispanic (all races) vs non-Hispanic white	1.371	0.792	2.373	.2592
Non-Hispanic black vs non-Hispanic white	1.667	0.818	3.398	.1595
Other non-Hispanic vs non-Hispanic white	1.156	0.526	2.541	.7180
Age (continuous)	0.740	0.494	1.108	.1436

Cox regression model adjusted for age, sex, and race/ethnicity as covariates with period of diagnosis as the main predictor.

Discussion

We noted that the population-level survival of pediatric patients with APL in the US has significantly improved over time and early mortality has improved in the most recent cohort. Several studies are available in the adult literature, indicating an improvement in population-level outcomes of APL over time, while corresponding information in the pediatric literature is sparse.[6,7] Chen et al previously reported on the population level outcomes of APL from 1975 to 2008 using the SEER database.[7] In this study, pediatric patients (age <20 years) constituted 10% of the overall cohort and had a 5-year relative survival of 52%. They also demonstrated that the survival improved significantly over time (from 22% in 1975-1999 to 73% in 2000-2008). Our study differs from the earlier study by focusing exclusively on pediatric patients and including a broader study period with a more recent cohort. The advent of advancements with regard to the disease biology and treatment options including the introduction of targeted agents such as ATRA and ATO has revolutionized the clinical care of these patients. In addition, careful monitoring and management of the complications of APL and better supportive care have also contributed much to this effect. Although this improvement in population-level survival is encouraging, there are opportunities for more research to improve the disease outcomes.

Although APL is seen in both children and adults, there are certain differences in their disease characteristics and management strategies. The rates of complete remission and survival are comparable between the 2 age groups, although early death rates have been reported to be lower in the pediatric population and the risk of relapse may be higher in very young children.[6,10-14] Based on prior published literature, pediatric APL tends to have a higher incidence of microgranular variant, BCR2 or BCR3 isoforms of PML-RARA, and a higher white cell count, which could negatively impact their outcomes.[11] Although anthracycline-based chemotherapy plays an important role along with ATRA for the management of pediatric APL, the current treatment regimens for adult APL often have ATRA and ATO without cytotoxic chemotherapy.[12] A few promising studies have demonstrated the feasibility of ATRA- and ATO-based combination therapy for pediatric APL with encouraging results.[15] Additionally, a risk-adapted approach and use of ATO consolidation to reduce the cumulative anthracycline exposure has also been shown to have good outcomes.[3,4] With more therapeutic advancements, the outcomes of pediatric APL are likely to improve more in future.

Age has been described as a predictor of survival in pediatric APL. A European multicenter trial of pediatric APL showed that patients aged 4 years and younger had a higher risk of relapse and adolescents (13-18 years) had a better survival.[11] Kutny et al showed that pediatric APL patients enrolled in CALGB 9710 trial did not show a significant difference in event-free survival based on their age.[16] Hispanics constituted 35% of our cohort, similar to prior reports suggesting an association between Hispanic ethnicity and APL, although our data are not focused on disease incidence.[17] In the present study, we did not find age, sex, or race/ethnicity to be significant predictors of overall survival on multivariate analysis. Prior studies in APL and acute myeloid

Table IV. Logistic regression model estimates for probability of early death (n = 553)

Predictors	Comparison	OR	Wald lower 95% confidence limit for aOR	Wald Upper 95% confidence limit for aOR	*P* value
Age		2.17	1.22	3.86	.0086
Cohort	1976-1989 vs 2010-2016	2.72	0.98	7.54	.0542
Cohort	1990-1999 vs 2010-2016	2.37	0.97	5.78	.0570
Cohort	2000-2009 vs 2010-2016	2.20	1.11	4.35	.0240
Race/ethnicity	Hispanic (all races) vs non-Hispanic white	1.22	0.66	2.27	.5232
	Non-Hispanic black vs non-Hispanic white	1.71	0.75	3.86	.1993
	Other non-Hispanic vs non-Hispanic white	0.61	0.20	1.86	.3886
Sex	Female vs male	0.85	0.50	1.46	.5559

Logistic regression model adjusted for age, sex, and race/ethnicity as covariates with period of diagnosis as the main predictor.

leukemia have shown varying results about the influence of sex and race on disease outcomes.[7,18,19] The reason for these variations is unclear and the intrinsic differences in the databases utilized adds to the complexities of cross-study comparisons. Additionally, variations in nonbiological factors aligning closely with these demographic characteristics, such as the support system, insurance status, and access to care, could have contributed to the differences in results.[20,21] We could not compare the outcomes of patients based on insurance status (insured vs uninsured) because most patients diagnosed from 2007 onward were insured. Prospective studies addressing the role of these factors would be able to provide a clear information about variables other than disease biology and treatment, which influence the disease outcomes. The improvement in survival noted in our study could be reflective of the effect of newer therapies introduced over time. ATRA received initial approval by the US Food and Drug Administration in 1995 and ATO was approved by the US Food and Drug Administration in 2000. However, the largest trial of ATRA for pediatric APL (AIDA0493) was published in 2005 and the first north American intergroup study of ATRA for pediatric APL (INT0129) was published in 2009.[5,22] Hence, the availability of these agents coincides with the improvement in outcomes seen from 2000 onward, although it is important to note that we do not have treatment-related information to make a definitive correlation.

Our study showed an improvement in early mortality in the most recent cohort compared with prior years. Early mortality is an important issue contributing to the adverse outcomes of APL resulting from complications such as hemorrhage, differentiation syndrome, and infections. In pediatric studies, early mortality has been reported to occur in 3%-8% of patients, which is relatively lesser as compared with adult APL.[6,10] A previous real-world pediatric APL study from the US showed that early mortality occurred in about 7% of patients and the mean time to first ATRA exposure increased with decreasing age.[23] This could be due to lesser awareness in considering APL in the differential diagnosis in children. Our data are limited by the nonavailability of information on treatment setting (academic vs community hospitals), interval between symptom onset and treatment initiation, and other disease- or treatment-related factors that could affect these outcomes. However, it is possible that the therapeutic advancements and better supportive care over time could have contributed to the improvement in early mortality noted in our study.

Study limitations include the retrospective design and the lack of information on clinical presentation, leukocyte count, minimal residual disease status, and treatment received. Additionally, we did not have information on disease relapse or complications.

The population-level outcomes of pediatric APL have continued to improve over time in the US, likely reflecting the clinical impact of diagnostic and therapeutic advancements. Early mortality continues to be an important adverse factor justifying the need for more measures to decrease its occurrence. Upcoming clinical trials investigating frontline chemotherapy free approaches in pediatric APL could improve the outcomes and needs to be investigated in future studies. ■

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50 Years Ago in *The Journal of Pediatrics*

Light Exposure to the Immature Eye

Sisson TRC, Glauser EM, Kuwabara T. Retinal changes produced by phototherapy. J Pediatr 1970;77:221-7.

The first indications that nonthermal retinal damage might exist were presented by Vos in 1962.[1] A few years later, in *The Journal*, Sisson et al published a study in which they examined the effects of phototherapy with blue fluorescent light on the retinas of newborn piglets to assess possible effects of phototherapy on the eyes of newborn infants. The use of phototherapy was first published by Cremer in 1958[2] and became more commonly used in the 1960s and 1970s.

Sisson et al examined the eyes 3 weeks after the piglets had been exposed to phototherapy for 72 hours, and also 1 eye that was only exposed for 12 hours, and found extensive retinal damage, which supported the hypothesis that eyes should be shielded during phototherapy. This and other studies stimulated Glass and Avery 15 years later to examine whether bright light in the nursery may contribute to retinopathy of prematurity.[3] They recommended to shield the eye from bright light but also warned that prolonged occlusive patching of the eye would produce visual deprivation and should be avoided. In 1998 Reynolds et al showed that light reduction did not prevent retinopathy of prematurity.[4] Sisson et al and other studies contributed to present practice of shielding the eye of infants born premature undergoing phototherapy and thus still have an impact on how we treat these infants.

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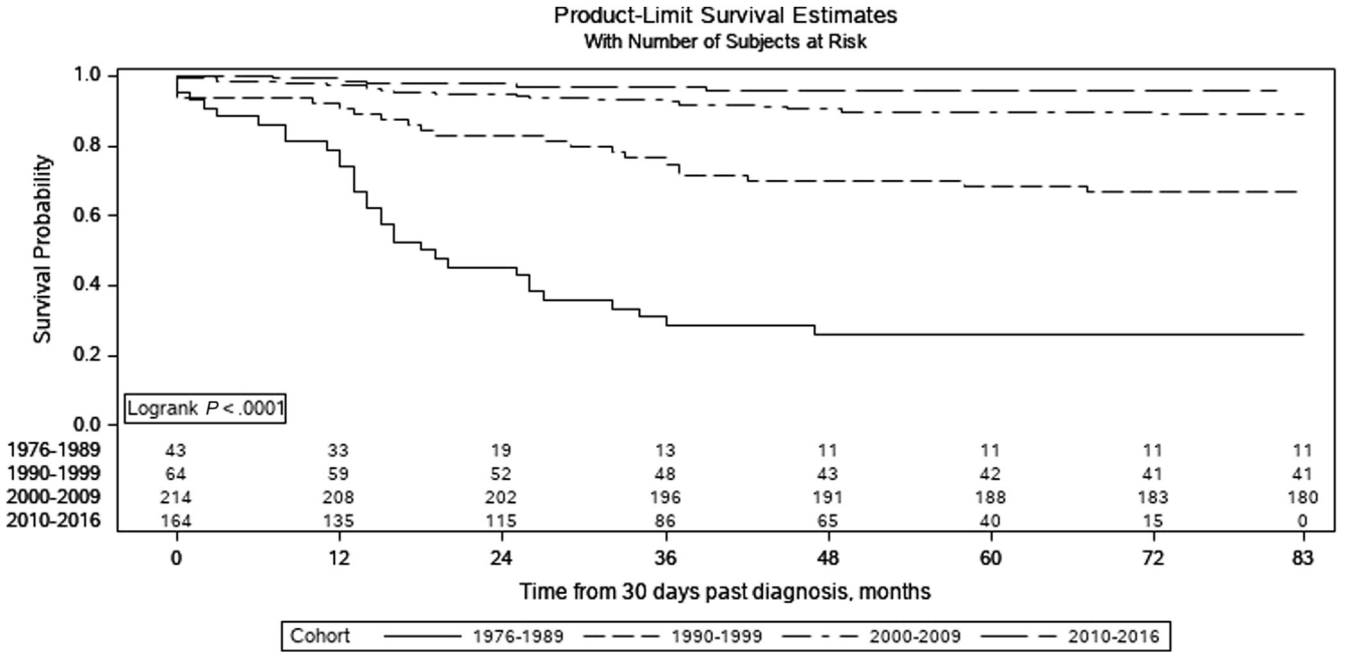

Figure 2. Overall survival after 1 month by period of diagnosis.

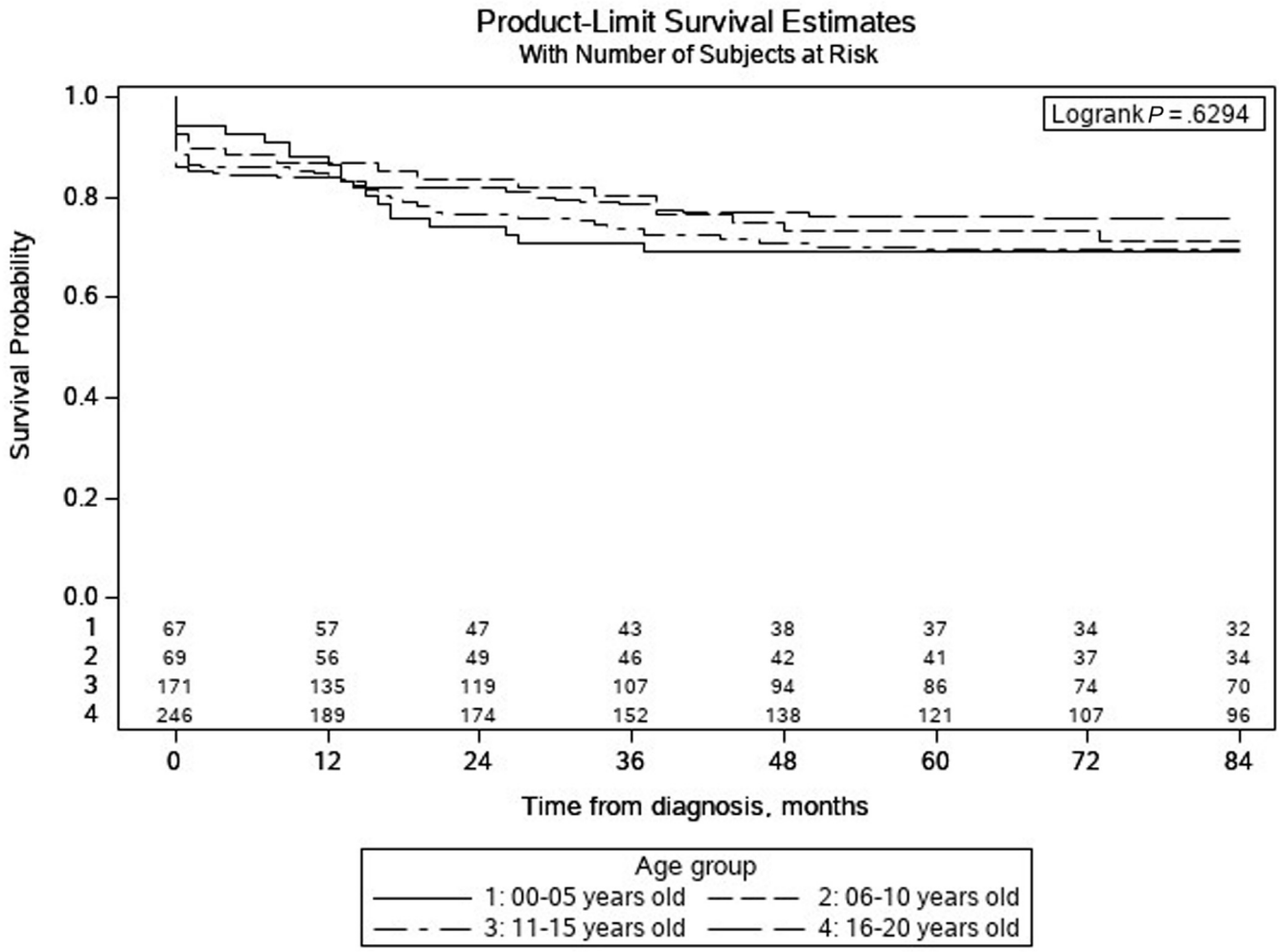

Figure 3. Overall survival by age.

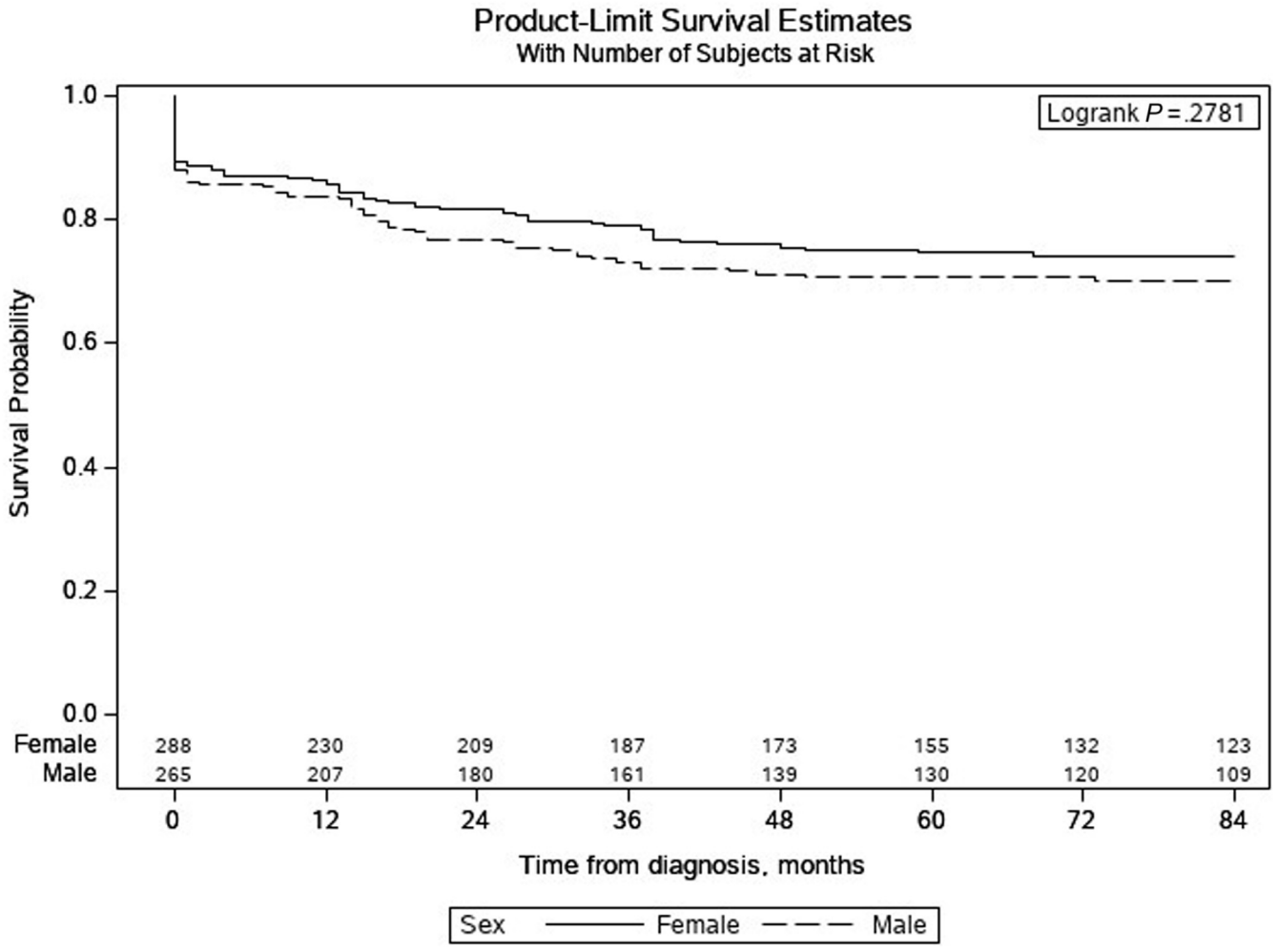

Figure 4. Overall survival by sex.

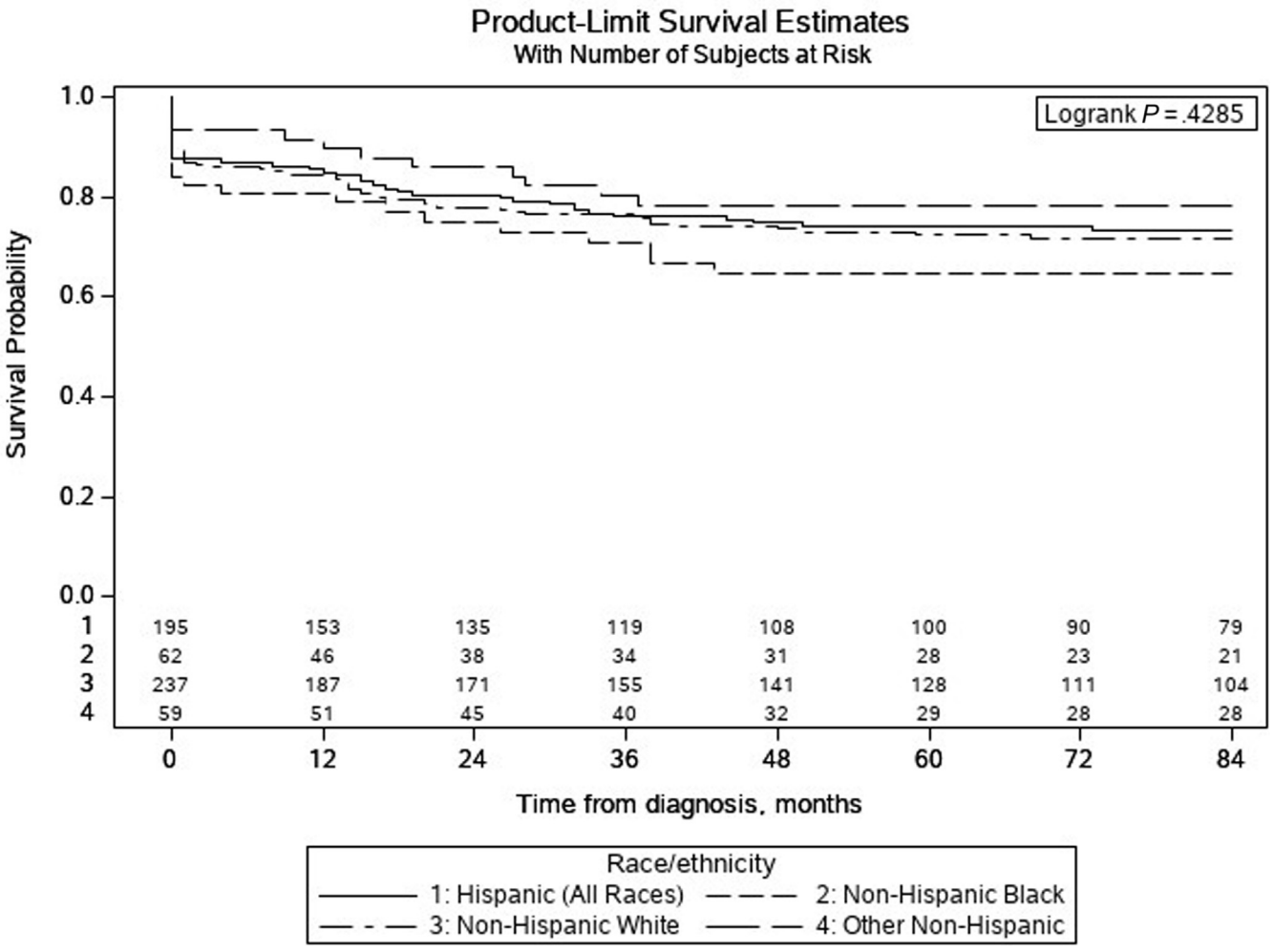

Figure 5. Overall survival by race/ethnicity.

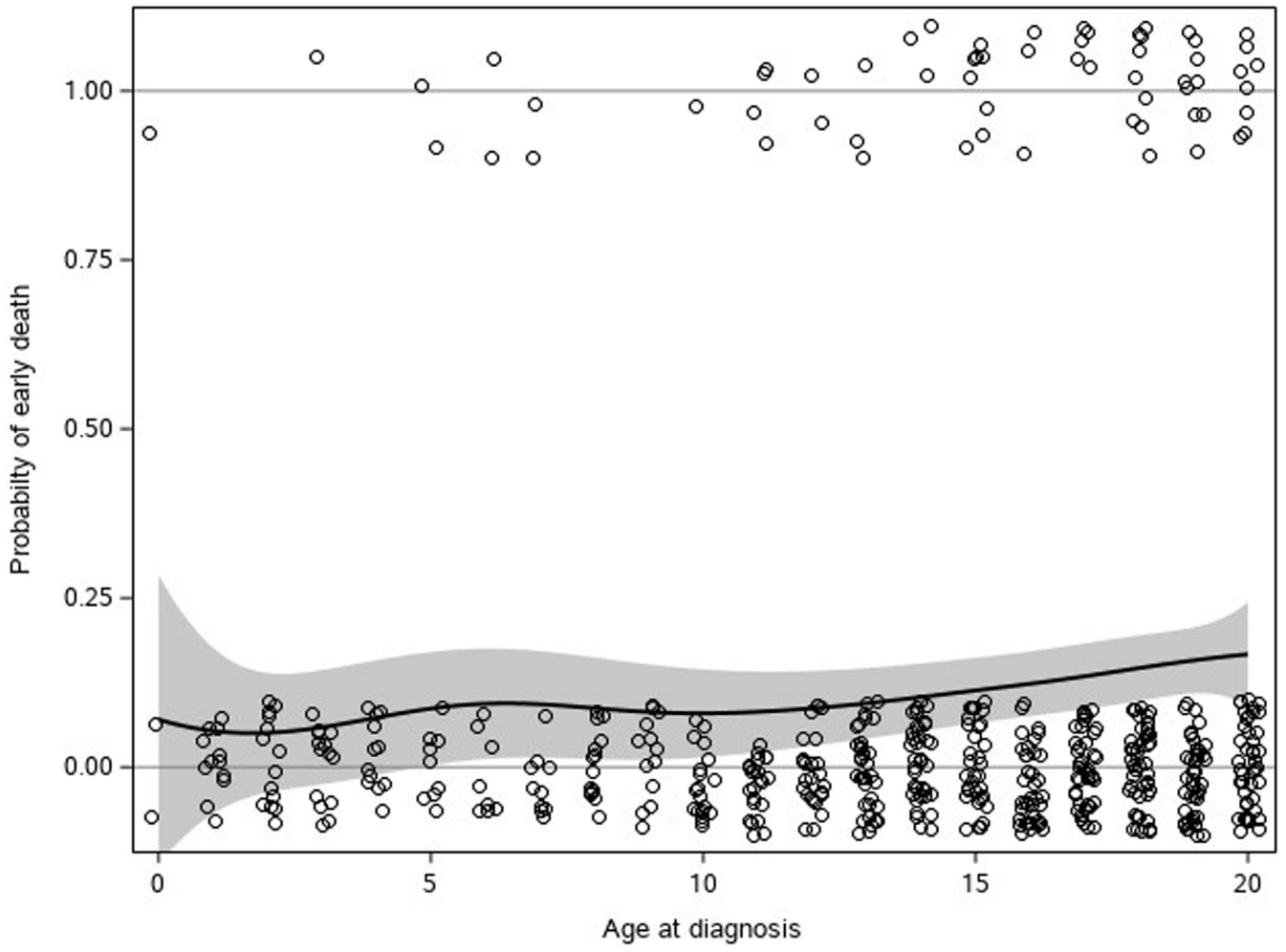

Figure 6. Effect of age on early mortality.

Table I. Test for the presence of breakpoints in the effect of calendar year on the outcomes

Outcomes	*P* value
Early death	.1819
Overall survival	.4893