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## Predictors of early death and survival among children, adolescents and young adults with acute myeloid leukaemia in California, 1988–2011: a population-based study

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### Abstract

A better understanding of factors associated with early death and survival among children, adolescents and young adults with acute myeloid leukaemia (AML) may guide health policy aimed at improving outcomes in these patients. We examined trends in early death and survival among 3935 patients aged 0 to 39 years with *de novo* AML in California during 1988–2011 and investigated the associations between sociodemographic and selected clinical factors and outcomes. Early death declined from 9.7% in 1988–1995 to 7.1% in 2004–2011 ( $P=0.062$ ), and survival improved substantially over time. However, 5-year survival was still only 50% (95% confidence interval 47%–53%) even in the most recent treatment period (2004–2011). Overall, the main factors associated with poor outcomes were older age at diagnosis, treatment at hospitals not affiliated with National Cancer Institute-designated cancer centres, and black race/ethnicity. For

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### AUTHOR CONTRIBUTIONS

R Abrahão, RC Ribeiro and THM Keegan designed the study, and R Abrahão led the writing and review of the manuscript. R Abrahão performed the statistical analyses and RH Keogh and DY Lichtensztajn advised on and reviewed the statistical analyses. RH Keogh, RC Ribeiro, DY Lichtensztajn, R Marcos-Gragera, BC Medeiros, MP Coleman and THM Keegan participated in the interpretation of data and drafting and critical review of the manuscript. All authors read and approved the final manuscript. R Abrahão had full access to all of the data in the study and takes responsibility for the decision to submit the manuscript for publication.

patients diagnosed during 1996–2011, survival was lower among those who lacked health insurance compared to those with public or private insurance. We conclude that mortality after AML remained strikingly high in California and increased with age. Possible strategies to improve outcomes include wider insurance coverage and treatment at specialized cancer centres.

### Keywords

acute myeloid leukaemia; survival; early death; population-based

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## INTRODUCTION

Acute myeloid leukaemia (AML) is a complex and highly heterogeneous disease. Without treatment, most patients die within weeks or months of diagnosis (Appelbaum, *et al* 2006). Survival among patients with AML has increased over the last 3 decades, mostly among patients younger than 60 years of age, but progress has now reached a plateau (Pritchard-Jones, *et al* 2013; Ribeiro 2014) and acute leukaemias, including AML, remain the leading cause of cancer deaths among patients aged 39 years or younger (Deschler and Lubbert 2006; Wingo, *et al* 2003). Although complete remission can be achieved in approximately 75% to 90% of patients younger than 60 years of age, approximately 35% to 50% of these patients experience relapse within the following 2 years (Burnett 2005; Hann, *et al* 2004). Disturbingly, children, adolescents and young adults who survive AML may suffer long-term debilitating complications of treatment, such as secondary malignancies, cardiovascular and neurocognitive dysfunctions, as well as severe psychosocial effects (Byrne, *et al* 2011; Dores, *et al* 2012; Mulrooney, *et al* 2008; Schultz, *et al* 2014; Sekeres, *et al* 2004; Sullivan, *et al* 2013).

Given the lack of population-based studies focusing on young patients with AML (Pulte, *et al* 2009), we aimed to evaluate trends in survival and early death (i.e., death occurring within 30 days of diagnosis) among patients aged 0 to 39 years with AML in California, and investigate sociodemographic and selected clinical factors associated with poor outcomes.

## PATIENTS AND METHODS

### Patients

Our data were obtained from the California Cancer Registry (CCR), which participates in the Survival Epidemiology and End Results (SEER) Programme of the National Cancer Institute (NCI). Reporting of all malignant neoplasms is compulsory in California, and the standard for completeness of ascertainment is at least 98% (Hayat, *et al* 2007). In addition to relevant variables available in the SEER datasets, the CCR provides information on hospital designation (i.e., whether the initial reporting hospital is affiliated with a NCI-designated cancer centre), whether the patient has undergone chemotherapy or haematopoietic stem cell transplantation (HSCT) and neighbourhood socioeconomic status (SES).

Ethics approval for human subject research was obtained from the Cancer Prevention Institute of California Institutional Review Board. As the analysis was based on state-mandated cancer registry data, the study was conducted in accordance with the waivers of

individual informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization.

We identified all patients aged 0 to 39 years who were diagnosed with de novo AML between 1 January 1988 and 31 December 2011, and excluded those with acute promyelocytic leukaemia, which has a much more favourable prognosis than the other subtypes of AML and was the focus of a separate study (Abrahão, *et al* 2015a). Information on patients with AML associated with Down syndrome (who also have a better prognosis) was only available in the CCR from 2010 onwards; prior to that, these cases were classified as 'AML not otherwise specified'. Therefore, it was not possible to study these patients separately.

To identify cases of AML diagnosed during 1988–2011, we used the following morphology codes from the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) (World Health Organization 2000): 9840, 9861, 9867, 9870–9874, 9891, 9895–9898, 9910, 9920, and 9931. We excluded patients diagnosed by autopsy or death certificate only ( $n = 12$ ), patients of non-Hispanic American Indian ( $n = 20$ ) or unknown ( $n = 18$ ) race/ethnicity and patients with a missing month of diagnosis ( $n = 22$ ). Patients who died on the day of diagnosis ( $n = 28$ ) were included. Of the 4007 patients reviewed, 3935 (98.2%) were included in the analyses. All the patients were followed from the date of diagnosis until death, loss to follow-up or the end of the study (31 December 2012), whichever occurred first.

### Demographic and clinical variables

We examined early death and survival with a comprehensive set of variables in order to identify the main factors associated with poorer prognosis among young patients (< 39 years of age). Age is independently associated with survival after AML, and a progressive survival decline is observed from 10 years of age (Gatta, *et al* 2014, Horibe, *et al* 2001, Ofran and Rowe 2014, Razzouk, *et al* 2006, Walter, *et al* 2011). Based on these observations, we categorized age in 4 groups (0–9, 10–19, 20–29, and 30–39 years). To evaluate trends in outcomes, we used 3 calendar periods of diagnosis (1988–1995, 1996–2003, and 2004–2011). Race/ethnicity was classified in 4 groups [non-Hispanic white (white), non-Hispanic black (black), Hispanic, and non-Hispanic Asian/Pacific Islander (Asian)]. Neighbourhood SES was divided into quintiles by using a previous developed index (Yost, *et al* 2001), which is based on block-level census data, and is considered an adequate surrogate to SES at the individual level (Glaser, *et al* 2014; Tao, *et al* 2014). Patients' health insurance status was routinely reported by the CCR from 1996 onwards and was categorized in 4 groups [uninsured, publicly insured, privately insured or unknown/not otherwise specified (NOS)]. Binary variables were sex (male/female) and initial care at hospitals affiliated with NCI-designated cancer centres (Y/N).

We provided descriptive information on chemotherapy and HSCT, that, like all treatment data collected by the CCR, is limited to the first course of treatment, with no details on treatment regimens or intensity. Information on HSCT was routinely reported from 2003 onwards; however, it was also abstracted for patients diagnosed during 1996–2002, when available.

## Statistical analysis

Our analyses investigated how the following variables representing sociodemographic and clinical characteristics were associated with early death and overall survival: age at diagnosis, treatment period, sex, race/ethnicity, neighbourhood SES, health insurance status, and treatment facility. All of the variables considered had a priori hypothesized or previously observed (Bradley, *et al* 2011, Patel, *et al* 2015a, Percival, *et al* 2015, Pulte, *et al* 2013, Walter, *et al* 2011, Wolfson, *et al* 2012) associations with early death or survival. We also hypothesized that sociodemographic factors would have a greater impact on survival in older versus younger patients and investigated this hypothesis by analysing the hazard of death by age group.

**Early death**—Chi-squared tests were used for testing whether early death differed among groups for each covariate. The Kruskal-Wallis test was also used for ordinal covariates (age group, neighbourhood SES and calendar period). We used multivariate logistic regression to obtain the odds ratios (ORs) for early death (death within 30 days of diagnosis) and the corresponding 95% confidence intervals (95% CIs) associated with sociodemographic and clinical characteristics. We used the likelihood ratio test as an overall significance test for the association of each independent variable with early death.

**Survival**—We estimated the overall (all causes) survival at 1, 5, and 10 years by using the Kaplan-Meier method and tested differences in survival across strata of each variable with the log-rank test (the log-rank test for trend was also estimated for ordinal variables). Twenty-eight patients who died on the day of diagnosis were considered to have a survival time of 1 day.

The 5-year survival in the 3 calendar periods examined and the 10-year survival in 1988–1995 and 1996–2003 were estimated using the traditional cohort-based approach, because most patients had been followed for at least 5 or 10 years, respectively, during these time periods. For patients who had all been followed up for at least 10 years, the classical cohort approach provided survival estimates using all the observed follow-up data. For patients with less than 5 (or 10) years of follow-up, we used the period approach (Brenner, *et al* 2004) to obtain a short-term prediction of their survival up to 5 (or 10) years after diagnosis on the assumption that their partial probabilities of survival will be the same as those observed during the most recent years for which follow-up data were available.

We used multivariate Cox regression to obtain the hazard ratios (HRs) and corresponding 95% CIs for each variable, and the likelihood ratio test as an overall significance test for the association of each independent variable with survival. The proportional hazard assumption, assessed by looking at Schoenfeld residuals, was met for all variables in the multivariate model. To investigate whether the association of survival with sociodemographic and clinical factors varied with age, we fitted separate Cox models by age group (0–9, 10–19, 20–29 and 30–39 years) and tested for interactions between age group and each variable using the likelihood ratio test. Statistical analyses were performed using Stata 13 software (StataCorp, College Station, TX), and a 2-sided *P* value of less than 0.05 was considered statistically significant.

## RESULTS

### Sociodemographic and clinical characteristics

Among 3935 patients, the median age at diagnosis was 23 years (range, 0–39 years), with a slight predominance of males (53.5%) (Table I). Most patients were white (41%) or Hispanic (39%) and were treated at hospitals that were not affiliated with NCI-designated cancer centres (74%). For patients diagnosed during 1996–2011, 85% had health insurance (46% had private insurance and 39% had public insurance), 4% were uninsured and 11% had unknown or not otherwise specified health insurance status.

Chemotherapy was administered to 93% of patients; it was recommended, but not given, to 2% of patients, and refused by 0.2% of patients (or their families). A total of 690 patients (26%) received HSCT; 324 (27%) of those diagnosed during 1996–2003 and 366 (30%) of those diagnosed during 2004–2011. Leukaemia was the cause of death in 88% of patients; a small percentage died of other (9%) or unknown (3%) causes. Of the deaths resulting from other causes, 3% were caused by infections (data not shown).

### Early death

In total, 332 patients (8.4%) died within 30 days of diagnosis. There was a trend towards a reduction in early death over time, from 9.7% in 1988–1995 to 8.6% in 1996–2003 to 7.1% in 2004–2011 ( $P = 0.062$ ) (Table I). Overall, in unadjusted analyses, early death was strongly associated with age, hospital designation, neighbourhood SES, and health insurance status (Table I). In multivariate analyses in which all variates were mutually adjusted (Table II), the odds of early death increased progressively with age: the OR for older patients (aged 30 to 39 years) was increased by 70% relative to that for younger patients (aged 0 to 9 years) (OR = 1.70, 95% CI 1.22–2.38). Patients treated at hospitals not affiliated with NCI-designated cancer centres had a higher risk of early death compared with those treated at hospitals affiliated with such centres (OR = 1.75, 95% CI 1.28–2.39). Uninsured patients diagnosed during 1996–2011 had an approximately 3 times greater risk of early death than privately insured patients (OR = 2.91, 95% CI 1.65–5.12); there was no evidence of such a difference between publicly and privately insured patients ( $P = 0.849$ ). Patients living in the lowest SES neighbourhoods had a significantly greater risk of early death than patients living in the highest SES neighbourhoods (OR = 1.57, 95% CI 1.05–2.34).

### Survival

Of 3935 patients included in the analysis, 2272 (58%) died over the course of follow-up. Approximately 93% of patients had confirmation of vital status within 18 months of the study end date. The median time to death for deceased patients was 0.9 years, the median follow-up time for surviving patients was 8.8 years, and the overall median follow-up time using reverse censoring (Schemper and Smith 1996) was 10.0 years. Overall survival improved substantially over time for all ages and racial/ethnic groups. Five-year survival increased from 32.9% (95% CI 30.3–35.5) in 1988–1995 to 50% (95% CI 47.0–52.9) in 2004–2011 (Table I). Based on the log-rank test, there was evidence of an association between worse survival and older age at diagnosis (Figure 1), black race/ethnicity, receipt of initial care in hospitals not affiliated with NCI-designated cancer centres, and, for patients

diagnosed during 1996–2011, lack of health insurance. In a multivariate Cox regression analysis in which all variables were mutually adjusted (Table III), we found an increased hazard of death for older patients compared with younger patients (30 to 39 vs. 0 to 9 years of age) (HR = 1.55, 95% CI 1.38–1.74), for black patients compared with white patients (HR = 1.27, 95% CI 1.08–1.49), and for patients who received initial care at hospitals not affiliated with NCI-designated cancer centres compared with those initially treated at such facilities (HR = 1.18, 95% CI 1.07–1.31). For patients diagnosed during 1996–2011, the hazard of death was higher among uninsured patients than among privately insured patients (HR = 1.34, 95% CI 1.01–1.78), with no evidence of a difference in hazard between privately and publicly insured patients ( $P = 0.429$ ).

When we fitted separate Cox models by age at diagnosis (Tables IV and V), we observed that the association between the hazard of death and sociodemographic and clinical factors varied by age group. Table IV presents Cox models for the factors available during 1988–2011 (all variables except health insurance status) by age group at diagnosis. Table V additionally includes health insurance status, but is limited to patients diagnosed during 1996–2011. For patients aged 0 to 9 years, we found no association between the risk of death and sociodemographic or clinical factors, whereas associations were found with advancing age (Table IV). Markedly, for patients aged 30 to 39 years, the hazard of death was substantially higher among those who received initial care at hospitals not affiliated with NCI-designated cancer centres (HR = 1.31, 95% CI 1.08–1.58) (Table IV) and, during 1996–2011, among uninsured patients (HR = 1.78, 95% CI 1.14–2.76) (Table V). We also observed an increased risk of death among black patients, particularly those aged 20 to 29 years (HR = 1.70, 95% CI 1.21–2.39) (Table IV). However, despite observed differences in associations between the explanatory variables and survival by age group, none of these were found to be statistically significant when tested for interactions between age group and each variable, and the results should therefore be interpreted with caution.

## DISCUSSION

Our study found evidence of a reduction in early death and an improvement in survival after AML over a 25-year period for patients of all age and racial/ethnic groups in California. Overall, early death and survival were associated with several sociodemographic and clinical factors, including age at diagnosis, race/ethnicity, neighbourhood SES, hospital designation, and health insurance status. Despite substantial improvements, approximately half of the patients died in the most recent treatment period (2004–2011).

We found worse survival among black patients than white patients, consistent with previous studies of AML and acute lymphoblastic leukaemia (ALL) (Abrahão, *et al* 2015b; Aplenc, *et al* 2006; Byrne, *et al* 2011; Patel, *et al* 2015b; Pulte, *et al* 2012; Pulte, *et al* 2013; Rubnitz, *et al* 2007; Sekeres, *et al* 2004). Results from several clinical trials at a single institution in the US showed survival in black children with AML to be similar to that in white children (Rubnitz, *et al* 2007). However, a recent trial at the same institution showed a trend towards worse outcomes in black children compared to those in white and Hispanic children (Rubnitz, *et al* 2007). It is not yet clear what factors accounted for the disparities in survival among black patients with AML that were observed in our and other studies. Black race/



ethnicity has been associated with both favourable and unfavourable cytogenetic subtypes (Rubnitz, *et al* 2007; Sekeres, *et al* 2004). It is possible that pharmacogenetic differences between black and white patients contribute to different responses to chemotherapy (Pui, *et al* 2004; Rubnitz, *et al* 2007). Another possibility is that black patients have had less access to chemotherapy and/or HSCT. A recent study using CCR data linked to hospital discharge data showed that the odds of receipt of HSCT and chemotherapy were lower among black than non-black patients (Patel, *et al* 2015a).

Interestingly, we found no evidence of differences in survival between Hispanic and white patients in any age group. This differs from the results of 2 consecutive clinical trials by the Children's Oncology Group (patients aged 0 to 21 years) (Aplenc, *et al* 2006), but is consistent with the population-based study mentioned above (Patel, *et al* 2015a) that found survival among Hispanics to be similar to that among white patients after adjustment for age (all ages included), and with paediatric clinical trials that showed favourable outcomes among Hispanic patients with AML (Rubnitz, *et al* 2007). These observations contrast with the worse survival observed among Hispanic children and adolescents with ALL in the US (Abrahão, *et al* 2015b; Goggins and Lo 2012; Lim, *et al* 2014; Pulte, *et al* 2013), and suggest that unfavourable biological characteristics are associated with survival after ALL, (Lim, *et al* 2014) but may not contribute, to the same extent, to the worse outcomes after AML. In fact, clinical trials have shown favourable cytogenetic characteristics among Hispanic children with AML (Rubnitz, *et al* 2007).

Clinical (Aplenc, *et al* 2006) and population-based studies (Patel, *et al* 2015a) that looked at the association of race/ethnicity with survival lacked information on SES. Our information on neighbourhood SES found a significant association between lower SES and higher early death, but there was no evidence of an association between neighbourhood SES and survival. This suggests that some patients with lower neighbourhood SES lacked access to optimal treatment during the critical initial days after AML diagnosis.

Our findings showed that survival was better among patients aged 0 to 9 years and there was no evidence of increased hazard of death associated with sociodemographic and clinical characteristics in this age group. However, among older patients, particularly those aged 30 to 39 years, we observed an association between increased risk of death and several sociodemographic and clinical factors, including treatment at hospitals not affiliated with NCI-designated cancer centres, lack of health insurance and black race/ethnicity. The diagnosis of AML in older patients may carry a worse prognosis and probably requires more intensive chemotherapy and, in some cases, HSCT. Consequently, these patients possibly have a higher probability of treatment-related complications (mainly haemorrhage and infection) requiring more aggressive treatment and long-term supportive care.

Recent studies have shown that the biology of paediatric AML differs from that of adult AML and that structural and numerical chromosome alterations have prognostic implications (Grimwade, *et al* 1998; Harrison, *et al* 2010; Tarlock and Meshinchi 2015). For instance, core-binding factor AML [CBF AML: t(8;21) and inv(16)/t(16;16)], which has a favourable prognosis, is more frequent in children and adolescents than in adults. In contrast, abnormalities of chromosomes 5 and 7 are more common in adults and are associated with a

dismal prognosis (Tarlock and Meshinchi 2015). Additionally, somatic mutations in selected genes, such as *FLT3*, *NPM1* and *CEBPA*, are known to have prognostic clinical significance in paediatric and adult AML. Whereas double *CEBPA* and isolated *NPM1* mutations are associated with a reduced risk of relapse and better survival (Ho, *et al* 2009; Yoon, *et al* 2015), patients with internal tandem mutations of *FLT3* (*FLT3*-ITD mutations) have a higher risk of relapse and worse survival and may benefit from receipt of HSCT (Schlenk, *et al* 2008). Adult AML has a higher prevalence of *FLT3*-ITD mutations compared to paediatric AML (27% vs. 12%) (Tarlock and Meshinchi 2015). These cytogenetic and genomic differences may partly account for the inferior outcomes we observed among older patients and explain the association between worse survival and sociodemographic and clinical factors. Hence, interventions to improve timely access to high-quality complex therapy and optimal supportive care for all individuals with AML have the potential to reduce mortality and morbidity, particularly among higher-risk and minority patients.

Other factors that may contribute to the worse outcomes among older patients with AML include the lower participation of adolescents and young adults in clinical trials or treatment at hospitals that are not affiliated with NCI-designated cancer centres compared with that of paediatric patients (Bleyer and Barr 2009). We had no information on patients' clinical trial enrolment, but our observations support the results from a previous study (Wolfson, *et al* 2012) showing that adolescents and young adults with cancer who were treated at hospitals affiliated with NCI-designated cancer centres had better outcomes than those treated at hospitals not affiliated with such centres.

Moreover, we found evidence of increased early death and worse survival among uninsured patients compared to privately or publicly insured patients. These results agree with recent studies that showed health insurance status to be independently associated with the risk of death (Bradley, *et al* 2011; Robbins, *et al* 2014; Rosenberg, *et al* 2014), and highlight the importance of health systems that provide timely access to adequate treatment (chemotherapy and, when recommended, HSCT) and optimal supportive care, including prophylaxis and control of invasive fungal infection.

Intensive chemotherapy regimens, improvements in supportive care, development of risk-adapted treatment strategies (through cytogenetic studies and early response to treatment as measured by minimal residual disease) and provision of HSCT to a greater number of high-risk patients are considered the primary causes of better outcomes in AML, rather than novel therapeutic agents (Ferrara and Schiffer 2013). Although improvements in HSCT have led to a significant decrease in transplant-related morbidity and mortality in patients with AML (Ferrara and Schiffer 2013), the role of HSCT remains controversial. With the progress in the use of chemotherapy and the improvement in risk assessment over the last 25 years, HSCT in first remission is not recommended for AML patients that have a favourable prognosis (CBF AML) (Carpenter, *et al* 2012), and the use of HSCT may be limited to intermediate-risk patients who experience relapse after undergoing initial therapy (Burnett, *et al* 2013).

Because AML is a complex disease characterized by morphological and cytogenetic heterogeneity, we believe that multiple factors may have contributed to the lower survival we



observed among older patients and those of black race/ethnicity. Further improvements in disease outcomes will also require the development of more effective and less toxic agents for each subtype of the disease (precision medicine) (Rubnitz and Inaba 2012). Conventional genetic and, more recently, genomic studies have played a key role in advancing the cure for ALL over a period of almost 30 years (Evans, *et al* 2013), and the same benefit is expected for AML. In the new era of basket trials [clinical trial design based on the hypothesis that the presence of a molecular marker predicts response to a targeted therapy regardless of tumour histology (Redig and Janne 2015)] and big data infrastructure (including access to electronic medical records and linkage of cancer registry data with insurance claims information) (Meyer and Basch 2015), national and international collaborations are fundamental to help to answer questions regarding treatment efficacy, toxicity and long-term survival.

Our study has several limitations. Hospital designation was limited to the location of care at the first reporting facility, so it is possible that some patients who were initially treated at one type of facility were subsequently treated at another. Nevertheless, the majority of our patients (90%) received at least part of their treatment at the reporting hospital. The CCR, like the majority of population-based cancer registries, does not collect information on patients' performance status, baseline cytogenetic risk assessment or relapse. Without these additional data, it was not possible to clearly investigate whether there was an association between the receipt of HSCT and survival. Although supplementary clinical information would have contributed additional important findings and explained some of the variability of our results, our study provided relevant information on survival and early death over a 25-year period in the most populous and racial/ethnically diverse state of the United States, using high-quality data. We have also provided important information on factors that may have influenced AML outcomes. To our knowledge, this is the first population-based study to consider the association between neighbourhood SES and outcomes (survival and early death) and to identify associations of several sociodemographic and clinical factors with survival, both overall and stratified by age group among children, adolescents and young adults with AML. Whereas clinical trials are essential to develop guidelines for the best therapeutic regimen (better efficacy with less toxicity), they provide data in less than 3% of the cancer population (Meyer and Basch 2015), although this proportion is usually higher among paediatric patients. In addition, clinical trials commonly report relatively short outcomes (i.e., event-free survival and 1 to 5 years overall survival). Our study included up to 10 years of survival estimates on virtually all patients in California, important information to evaluate long-term outcomes and excess mortality after treatment.

In conclusion, survival after AML increased over time among children, adolescents and young adults, but 5-year survival was still only 50% or less in the most recent treatment period (2004–2011). We identified subgroups with a higher risk of death from the disease, including those aged 10 to 39 years, uninsured patients, those who received initial care at hospitals not affiliated with NCI-designated cancer centres and those of black race/ethnicity. At the population-based level, strategies to address the high burden of AML, especially among adolescents and young adults, may include wider insurance coverage and treatment at specialized cancer centres.

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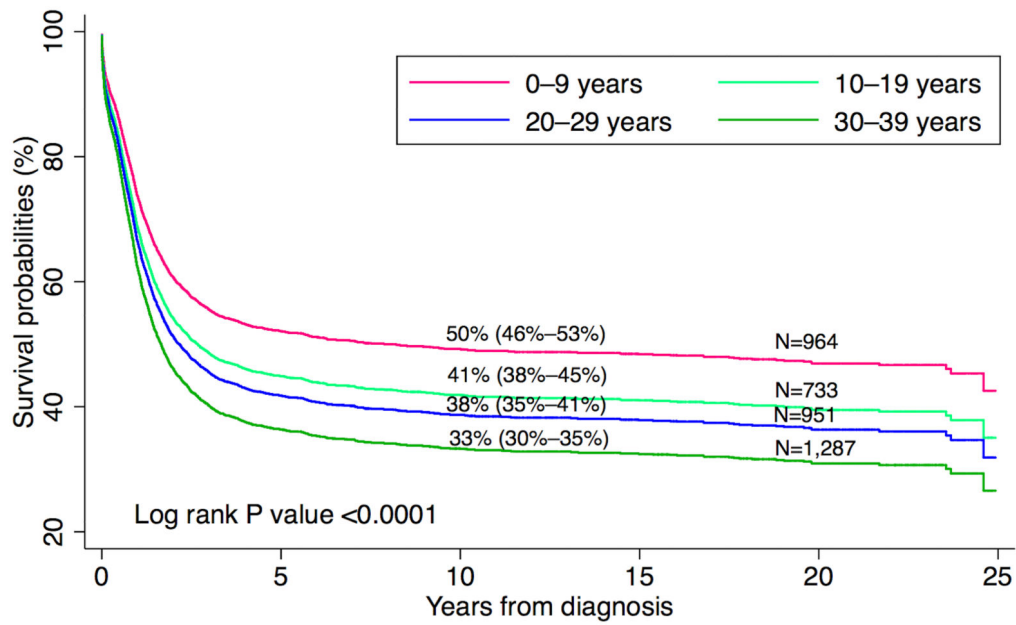
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**Figure 1.** Overall survival after acute myeloid leukaemia by age group at diagnosis, in California, 1988–2011 (percentages in the graph correspond to 10-year survival)



Patient characteristics, early death and overall survival in patients aged 0 to 39 years with acute myeloid leukaemia in California, 1988–2011.

**Table 1**

Characteristics	Total N (%)	Early death N (%)	<i>P</i> <sup>a</sup>	1-year OS (95% CI)	5-year OS (95% CI)	10-year OS* (95% CI)	<i>P</i> <sup>b</sup>
<b>Total</b>	3935 (100)	332 (8.4)		66.8 (65.3–68.3)	42.8 (41.2–44.4)	39.6 (38.0–41.3)	
<b>Calendar period</b>							
1988–1995	1303 (33.1)	126 (9.7)		59.3 (56.6–62.0)	32.9 (30.3–35.5)	30.7 (28.3–33.3)	
1996–2003	1299 (33.0)	111 (8.6)		68.1 (65.4–70.5)	45.8 (43.0–48.5)	42.4 (39.6–45.1)	
2004–2011	1333 (33.9)	95 (7.1)	0.0620/0.0626	72.8 (70.3–75.1)	50.0 (47.0–52.9)	45.2 (42.5–47.9)	<0.0001/<0.0001
<b>Age at diagnosis, years</b>							
0–9	964 (24.5)	55 (5.7)		73.2 (70.3–75.9)	52.4 (49.1–55.6)	50.0 (46.1–52.9)	
10–19	733 (18.6)	52 (7.1)		69.8 (66.3–73.0)	44.7 (40.9–48.4)	41.4 (37.6–45.2)	
20–29	951 (24.2)	94 (9.9)		64.8 (61.6–67.7)	40.4 (37.2–43.7)	37.9 (34.6–41.1)	
30–39	1287 (32.7)	131 (10.2)	<0.0001/0.0003	61.7 (58.9–64.3)	36.2 (33.5–38.9)	32.6 (29.9–35.4)	<0.0001/<0.0001
Median	23	27					
<b>Race/ethnicity</b>							
Non-Hispanic white	1607 (40.8)	131 (8.2)		65.4 (63.0–67.7)	44.3 (41.8–46.7)	40.8 (38.2–43.3)	
Non-Hispanic black	276 (7.0)	27 (9.8)		60.7 (54.6–66.1)	33.1 (27.4–38.8)	31.5 (25.8–37.2)	
Hispanic	1545 (39.3)	147 (9.5)		68.2 (65.8–70.5)	42.8 (40.2–45.4)	39.6 (36.9–42.3)	
Asian/Pacific Islander	507 (12.9)	27 (5.3)	0.0230	70.2 (65.9–74.0)	42.8 (38.3–47.3)	40.3 (35.7–44.8)	0.0087
<b>Sex</b>							
Male	2106 (53.5)	188 (8.9)		66.8 (64.7–68.8)	41.8 (39.6–44.0)	39.0 (36.8–41.2)	
Female	1829 (46.5)	144 (7.9)	0.2360	66.7 (64.5–68.9)	43.9 (41.6–46.3)	40.4 (38.0–42.8)	0.3151
<b>Initial care at hospitals affiliated with NCI-designated cancer centres</b>							
Yes	1039 (26.4)	53 (5.1)		72.3 (69.5–75.0)	49.4 (46.2–52.5)	46.8 (43.5–50.0)	
No	2896 (73.6)	279 (9.6)	<0.0001	64.8 (63.0–66.5)	40.4 (38.6–42.3)	37.1 (35.2–39.0)	<0.0001

Characteristics	Total N (%)	Early death N (%)	<i>P<sup>a</sup></i>	1-year OS (95% CI)	5-year OS (95% CI)	10-year OS* (95% CI)	<i>P<sup>b</sup></i>
<b>Neighbourhood socioeconomic status (quintiles)</b>							
1. Lowest 20%	986 (25.1)	108 (11.0)		65.1 (62.0–68.4)	42.1 (38.9–45.4)	38.8 (35.4–42.1)	
2.	826 (21.0)	61 (7.9)		68.3 (65.0–71.4)	41.0 (37.5–44.5)	37.7 (34.2–41.2)	
3. Middle 20%	783 (19.9)	64 (8.2)		64.8 (61.3–68.0)	40.3 (36.7–43.8)	37.1 (33.5–40.6)	
4.	714 (18.1)	57 (8.0)		68.0 (64.4–71.3)	46.2 (42.4–50.0)	42.9 (39.0–46.7)	
5. Highest 20%	626 (15.9)	42 (6.7)	0.0180/0.0178	68.4 (64.6–71.9)	45.5 (41.4–49.4)	43.1 (39.0–47.1)	0.1446/0.0338
<b>Health insurance status (limited to patients diagnosed in 1996–2011, N = 2632)</b>							
None	99 (3.8)	21 (21.2)		56.3 (45.7–65.7)	37.9 (27.7–48.0)	37.9 (27.7–48.0)	
Public	1038 (39.4)	78 (7.5)		71.9 (69.0–74.5)	47.6 (44.4–50.9)	43.8 (40.3–47.2)	
Private	1207 (45.9)	86 (7.1)		71.0 (68.3–73.5)	49.9 (47.0–52.8)	46.5 (43.5–49.5)	
Unknown/NOS	288 (10.9)	21 (7.3)	< 0.0001	67.9 (62.1–73.0)	42.6 (36.6–48.4)	37.1 (31.1–43.2)	0.0045

Abbreviations: OS, overall survival; CI, confidence interval; NOS, not otherwise specified; NCI, National Cancer Institute.

<sup>a</sup>The chi-squared was used to test whether early death differs among groups for each variable. For ordinal variables, the Kruskal-Wallis test also is reported (value on the right).

<sup>b</sup>The log-rank was used to test differences in survival across strata for each variable. The log-rank test for trend also is reported for ordinal variables (value on the right)

\*Ten-year survival during 2004–2011 was estimated using the period approach.

Relationship of sociodemographic and clinical factors to early death in patients aged 0 to 39 years with acute myeloid leukaemia in California, 1988–2011

**Table II**

Characteristics	Adjusted ORI (95% CI) 1988–2011	P-value*	Adjusted OR2 (95% CI) 1996–2011	P-value*	Adjusted OR3 (95% CI) 1996–2011	P-value*
<b>Calendar period</b>						
1988–1995	1.38 (1.04–1.83)		N/A		N/A	
1996–2003	1.22 (0.92–1.63)		1.23 (0.92–1.64)		1.20 (0.90–1.61)	
2004–2011	1 (reference)	0.0799	1 (reference)	0.1552	1 (reference)	0.2208
<b>Sex</b>						
Male	1.11 (0.88–1.40)		1.21 (0.91–1.62)		1.20 (0.90–1.61)	
Female	1 (reference)	0.3656	1 (reference)	0.1908	1 (reference)	0.2153
<b>Age at diagnosis, years</b>						
0–9	1 (reference)		1 (reference)		1 (reference)	
10–19	1.21 (0.82–1.40)		1.16 (0.90–2.76)		1.13 (0.70–1.81)	
20–29	1.64 (1.16–2.34)		1.58 (1.03–2.42)		1.44 (0.93–2.21)	
30–39	1.70 (1.22–2.38)	0.0049	1.36 (0.89–2.06)	0.1743	1.27 (0.84–1.94)	0.3915
<b>Race/ethnicity</b>						
Non-Hispanic white	1 (reference)		1 (reference)		1 (reference)	
Non-Hispanic black	1.15 (0.74–1.79)		1.07 (0.58–1.97)		1.06 (0.58–1.96)	
Hispanic	1.14 (0.86–1.49)		1.22 (0.86–1.73)		1.12 (0.78–1.61)	
Asian/Pacific Islander	0.65 (0.42–0.99)	0.0599	0.66 (0.38–1.15)	0.1533	0.66 (0.38–1.14)	0.2791
<b>Neighbourhood socioeconomic status (quintiles)</b>						
1. Lowest 20%	1.57 (1.05–2.34)		1.58 (0.90–2.76)		1.54 (0.87–2.72)	
2.	1.04 (0.68–1.57)		1.29 (0.73–2.27)		1.28 (0.72–2.26)	
3. Middle 20%	1.18 (0.78–1.77)		1.51 (0.86–1.73)		1.53 (0.87–2.69)	
4.	1.19 (0.78–1.81)		1.54 (0.87–2.70)		1.58 (0.90–2.80)	

Characteristics	Adjusted OR1 (95% CI) 1988–2011	P-value*	Adjusted OR2 (95% CI) 1996–2011	P-value*	Adjusted OR3 (95% CI) 1996–2011	P-value*
5. Highest 20%	1 (reference)	0.0934	1 (reference)	0.4512	1 (reference)	0.4411
<b>Initial care at hospitals affiliated with NCI-designated cancer centres</b>						
Yes	1 (reference)		1 (reference)		1 (reference)	
No	1.75 (1.28–2.39)	0.0002	1.96 (1.32–2.92)	0.0004	1.99 (1.33–2.97)	0.0004
<b>Health insurance status (limited to patients diagnosed in 1996–2011, N=2632)</b>						
Uninsured	N/A		N/A		2.91 (1.65–5.12)	
Public	N/A		N/A		1.03 (0.73–1.46)	
Private	N/A		N/A		1 (reference)	
Unknown/NOS	N/A	N/A	N/A	N/A	1.04 (0.01–0.43)	0.0046

Abbreviations: OR, odds ratio; CI, confidence interval; NOS, not otherwise specified; NCI, National Cancer Institute. OR1: adjusted model without insurance (1988–2011); OR2: adjusted model without insurance (1996–2011); OR3: adjusted model without insurance (1988–2011); OR2: adjusted model without insurance (1996–2011).

\*Likelihood ratio test.

Relationship of sociodemographic and clinical factors to the hazard of death after acute myeloid leukaemia in patients aged 0 to 39 years in California, 1988–2011

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**Table III**

Characteristics	Adjusted HR1 (95% CI) 1988–2011	P-value*	Adjusted HR2 (95% CI) 1996–2011	P-value*	Adjusted HR3 (95% CI) 1996–2011	P-value*
<b>Calendar period</b>						
1988–1995	1.58 (1.43–1.76)		N/A		N/A	
1996–2003	1.14 (1.03–1.27)		1.14 (1.02–1.27)		1.12 (1.00–1.25)	
2004–2011	1.0 (reference)	<0.0001	1.0 (reference)	0.0211	1.0 (reference)	0.0460
<b>Age at diagnosis, years</b>						
0–9	1.0 (reference)		1.0 (reference)		1.0 (reference)	
10–19	1.23 (1.07–1.40)		1.28 (1.08–1.52)		1.28 (1.07–1.51)	
20–29	1.34 (1.18–1.52)		1.39 (1.18–1.64)		1.38 (1.17–1.62)	
30–39	1.55 (1.38–1.74)	<0.0001	1.49 (1.28–1.74)	<0.0001	1.49 (1.28–1.74)	<0.0001
<b>Race/ethnicity</b>						
Non-Hispanic white	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Non-Hispanic black	1.27 (1.08–1.49)		1.33 (1.08–1.65)		1.34 (1.08–1.65)	
Hispanic	1.05 (0.95–1.16)		1.10 (0.96–1.25)		1.08 (0.94–1.24)	
Asian/Pacific Islander	0.98 (0.86–1.13)	0.0318	1.00 (0.83–1.18)	0.0505	1.00 (0.84–1.19)	0.0629
<b>Sex</b>						
Male	1.03 (0.95–1.12)		0.99 (0.89–1.10)		0.99 (0.89–1.10)	
Female	1.0 (reference)	0.4806	1.0 (reference)	0.8900	1.0 (reference)	0.8549
<b>Neighbourhood socioeconomic status (quintiles)</b>						
1. Lowest 20%	1.14 (0.99–1.31)		1.23 (1.01–1.49)		1.22 (1.00–1.48)	
2.	1.10 (0.95–1.27)		1.20 (1.00–1.46)		1.20 (0.99–1.45)	
3. Middle 20%	1.13 (0.98–1.30)		1.30 (1.08–1.58)		1.31 (1.08–1.59)	

Characteristics	Adjusted HR1 (95% CI) 1988–2011	P-value*	Adjusted HR2 (95% CI) 1996–2011	P-value*	Adjusted HR3 (95% CI) 1996–2011	P-value*
4.	1.01 (0.87–1.15)		1.07 (0.88–1.30)		1.07 (0.88–1.31)	
5. Highest 20%	1.0 (reference)	0.1868	1.0 (reference)	0.0490	1.0 (reference)	0.0453
<b>Initial care at hospitals affiliated with NCI-designated cancer centres</b>						
Yes	1.0 (reference)		1.0 (reference)		1.0 (reference)	
No	1.18 (1.07–1.31)	0.0009	1.26 (1.11–1.43)	0.0004	1.27 (1.11–1.45)	0.0002
<b>Health insurance status (limited to patients diagnosed in 1996–2011, N=2632)</b>						
None	N/A		N/A		1.34 (1.01–1.78)	
Public	N/A		N/A		1.05 (0.93–1.19)	
Private	N/A		N/A		1.0 (reference)	
Unknown/NOS	N/A		N/A		N/A	0.0204

Abbreviations: HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; NCI, National Cancer Institute. HR1: adjusted model without insurance, 1988–2011; HR2: adjusted model without insurance, 1996–2011; HR3: adjusted model with insurance, 1996–2011.

\*Likelihood ratio test.



Relation of sociodemographic and clinical factors to the hazard of death after acute myeloid leukaemia by age group at diagnosis, California, 1988–2011

Table IV

Characteristics (Total = 3935)	HR1 (95% CI) 0–9 years N = 964	P-value*	HR2 (95% CI) 10–19 years N = 733	P-value*	HR3 (95% CI) 20–29 years N = 951	P-value*	HR4 (95% CI) 30–39 years N = 1287	P-value*
<b>Calendar period</b>								
1988–1995	1.84 (1.45–2.34)		1.52 (1.19–1.93)		1.29 (1.05–1.59)		1.71 (1.44–2.04)	
1996–2003	1.36 (1.07–1.73)		1.27 (0.99–1.63)		0.95 (0.76–1.18)		1.14 (0.95–1.36)	
2004–2011	1.0 (reference)	<0.0001	1.0 (reference)	0.0034	1.0 (reference)	0.0049	1.0 (reference)	<0.0001
<b>Race/ethnicity</b>								
Non-Hispanic white	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Non-Hispanic black	1.22 (0.86–1.74)		1.19 (0.81–1.74)		1.70 (1.21–2.39)		1.19 (0.92–1.54)	
Hispanic	1.02 (0.82–1.28)		1.06 (0.83–1.35)		1.05 (0.86–1.30)		1.10 (0.93–1.30)	
Asian/Pacific Islander	0.79 (0.57–1.09)	0.2468	1.16 (0.84–1.60)	0.7294	1.28 (0.99–1.64)	0.0122	0.84 (0.67–1.05)	0.0821
<b>Sex</b>								
Male	0.93 (0.77–1.12)		0.89 (0.73–1.08)		1.17 (0.99–1.38)		1.06 (0.92–1.21)	
Female	1.0 (reference)	0.4455	1.0 (reference)	0.2287	1.0 (reference)	0.0734	1.0 (reference)	0.4152
<b>Neighbourhood socioeconomic status (quintiles)</b>								
1. Lowest 20%	0.88 (0.63–1.22)		1.11 (0.80–1.53)		1.26 (0.94–1.68)		1.19 (0.94–1.51)	
2.	1.07 (0.77–1.47)		0.96 (0.69–1.32)		1.03 (0.77–1.38)		1.21 (0.96–1.53)	
3. Middle 20%	0.86 (0.63–1.20)		0.93 (0.66–1.30)		1.14 (0.86–1.52)		1.31 (1.05–1.53)	
4.	0.83 (0.59–1.17)		0.82 (0.58–1.16)		0.84 (0.62–1.14)		1.31 (1.04–1.64)	
5. Highest 20%	1.0 (reference)	0.4063	1.0 (reference)	0.4579	1.0 (reference)	0.0583	1.0 (reference)	0.1260
<b>Initial care at hospitals affiliated with NCI-designated cancer centres</b>								
Yes	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
No	1.10 (0.91–1.32)	0.3314	1.29 (1.03–1.61)	0.0220	1.11 (0.90–1.37)	0.3310	1.31 (1.08–1.58)	0.0042

Abbreviations: HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; NCI, National Cancer Institute.

\*Likelihood ratio test.

Relationship of sociodemographic and clinical factors to the hazard of death after acute myeloid leukaemia by age group at diagnosis, including health insurance status, California, 1996–2011

**Table V**

Characteristics (Total = 2632)	HR1 (95% CI) 0–9 years N = 671	P-value*	HR2 (95% CI) 10–19 years N = 510	P-value*	HR3 (95% CI) 20–29 years N = 619	P-value*	HR4 (95% CI) 30–39 years N = 832	P-value*
<b>Calendar period</b>								
1996–2003	1.31 (1.02–1.68)		1.28 (0.99–1.64)		0.92 (0.74–1.15)		1.13 (0.94–1.36)	
2004–2011	1.0 (reference)	0.0308	1.0 (reference)	0.0580	1.0 (reference)	0.4640	1.0 (reference)	0.2000
<b>Race/ethnicity</b>								
Non-Hispanic white	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Non-Hispanic black	1.63 (1.04–2.57)		1.23 (0.74–2.05)		1.95 (1.17–3.25)		1.11 (0.78–1.56)	
Hispanic	1.27 (0.93–1.72)		1.05 (0.76–1.44)		1.17 (0.88–1.56)		0.99 (0.79–1.24)	
Asian/Pacific Islander	0.87 (0.55–1.36)	0.0821	1.01 (0.66–1.55)	0.8872	1.40 (1.01–1.92)	0.0392	0.83 (0.62–1.11)	0.4981
<b>Sex</b>								
Male	0.89 (0.70–1.12)		0.84 (0.65–1.08)		1.08 (0.86–1.35)		1.06 (0.88–1.27)	
Female	1.0 (reference)	0.3220	1.0 (reference)	0.1688	1.0 (reference)	0.5054	1.0 (reference)	0.5343
<b>Neighbourhood socioeconomic status (quintiles)</b>								
1. Lowest 20%	0.92 (0.59–1.43)		1.12 (0.71–0.78)		1.37 (0.92–2.04)		1.34 (0.95–1.88)	
2.	1.16 (0.76–1.77)		0.92 (0.59–1.44)		1.03 (0.69–1.53)		1.56 (1.14–2.15)	
3. Middle 20%	1.02 (0.67–1.56)		0.99 (0.64–1.53)		1.21 (0.82–1.78)		1.76 (1.28–2.42)	
4.	0.92 (0.59–1.45)		0.87 (0.54–1.40)		0.77 (0.51–1.16)		1.60 (1.17–2.20)	
5. Highest 20%	1.0 (reference)	0.6758	1.0 (reference)	0.7838	1.0 (reference)	0.0281	1.0 (reference)	0.0035
<b>Initial care at hospitals affiliated with NCI-designated cancer centres</b>								
Yes	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
No	1.12 (0.88–1.43)	0.3512	1.44 (1.09–1.90)	0.0078	1.24 (0.93–1.66)	0.1414	1.39 (1.08–1.80)	0.0095

Characteristics (Total = 2632)	HR1 (95% CI) 0-9 years N = 671	P-value*	HR2 (95% CI) 10-19 years N = 510	P-value*	HR3 (95% CI) 20-29 years N = 619	P-value*	HR4 (95% CI) 30-39 years N = 832	P-value*
<b>Health insurance status</b>								
None	1.60 (0.63-4.02)		1.78 (0.85-3.75)		0.94 (0.57-1.55)		1.78 (1.14-2.76)	
Public	0.93 (0.69-1.25)		1.21 (0.90-1.64)		0.99 (0.77-1.27)		1.10 (0.90-1.36)	
Private	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Unknown/NOS	1.21 (0.83-1.75)	0.4384	1.35 (0.92-1.99)	0.2399	1.45 (1.02-2.07)	0.1965	1.17 (0.86-1.59)	0.0986

Abbreviations: HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; NCI, National Cancer Institute.

\*Likelihood ratio test.