Acute leukaemia in children, adolescents and young adults in California: trends and inequalities in early death and survival during 1988–2011

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Declaration of authorship

I, Renata Abrahão, confirm that the work presented in this thesis is my own. When information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Survival after acute paediatric (0–14 years), adolescent (15–19 years) and young adult (20–39 years) leukaemia has improved substantially over the last five decades, particularly for acute lymphoblastic leukaemia (ALL) and acute promyelocytic leukaemia, a subtype of acute myeloid leukaemia. This progress represents one of the most successful achievements in the history of medicine and has been attributed to the development of effective chemotherapy regimens, improvement in supportive care, better risk stratification, use of targeted therapies, and advances in haematopoietic stem cell transplantation.

Currently, long-term survival for children diagnosed with acute lymphoblastic leukaemia is 80%–90% in developed countries. Strikingly, survival among adolescents and young adults with this disease is about 60% and 40% respectively. In addition, in these countries, 5-year survival for young patients with acute myeloid leukaemia (excluding acute promyelocytic leukaemia) remains approximately 60% in the modern era of treatment.

This project aimed to evaluate how survival and, when appropriate, early death (death occurring within 30 days of diagnosis) after acute leukaemia varied during almost 25 years in California, the most populous and racially/ethnically diverse state in the United States (US). A second aim was to investigate the association between sociodemographic and selected clinical factors and outcomes. Using high-quality data from the California Cancer Registry, I evaluated survival trends from acute lymphoblastic leukaemia among patients aged 0–19 years, and survival and early death trends after acute myeloid leukaemia among patients aged 0–39 years. I also investigated whether early death has decreased among young patients after the approval

by the US Food and Drug Administration of all-*trans* retinoic acid (ATRA) for the treatment of acute promyelocytic leukaemia.

The overall results of this thesis showed improvement in survival over time for all age groups and subtypes of leukaemia. Early death after acute promyelocytic and myeloid leukaemias declined during the study period. However, these outcomes varied widely by age at diagnosis and were associated with sociodemographic and clinical factors.

Racial/ethnical survival inequalities were identified and found to persist even after adjustment for other covariates. These inequalities were more marked among patients of Hispanic (acute lymphoblastic leukaemia) and black race/ethnicity (for acute lymphoblastic and myeloid leukaemias). Patients living in lower socioeconomic neighbourhoods had worse survival than those living in higher socioeconomic neighbourhoods (for acute lymphoblastic and myeloid leukaemias).

Early death and worse survival were associated with initial care at hospitals not affiliated with National Cancer Institute-designated cancer centres (for acute myeloid leukaemia) and lack of health insurance (for acute myeloid and promyelocytic leukaemias). Intriguingly, over the 25-year study period, adolescents and young adults with acute leukaemia continued to have worse survival than children. These results suggest that lack of timely access to treatment and suboptimal care have influenced outcome among vulnerable patients.

In conclusion, survival and early death after acute leukaemia has greatly improved among young patients in California. However, inequalities in outcomes remain and are likely a result of multiple factors. My studies highlight

the importance of population-based data to reveal the actual burden of the disease in this population and help clinicians, policy makers, government, and researchers better understand the predictors of outcomes. I expect my work to contribute to the development of strategies aimed at improving survival from acute leukaemia, especially among vulnerable and disadvantaged patients.

This thesis is dedicated to my family and friends who have always encouraged me to pursue my dreams. I also want to honour my collaborators who supported my work wherever they were and whenever I needed.

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I am very grateful to my colleagues at the Cancer Prevention Institute of California who not only opened the door of the institution for me and provided me the data that are the foundation of this thesis, but were also a constant source of inspiration, knowledge and support. Special thanks to Drs Theresa Keegan, Daphne Lichtensztajn and Sally Glaser.

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Abbreviations

ACA	Patient Protection and Affordable Care Act
AIEOP	Associazione Italiana Ematologia Oncologia Pediatrica
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
AMLCG	Acute Myeloid Leukaemia Cooperative Group
AMLSG	Acute Myeloid Leukaemia Study Group
ANLL	Acute non-lymphoblastic leukaemia
APL	Acute promyelocytic leukaemia
ATRA	All-*trans* retinoic acid
BMF	Berlin-Frankfurt-Münster Study Group
CALGB	Cancer and Leukaemia Group B
CBF	Core-binding factor
CCG	Children's Cancer Group
CCR	California Cancer Registry
CCS	California Children's Services
CI	Confidence interval
CNS	Central nervous system
COG	Children's Oncology Group
CRLF2	Cytokine receptor-like factor 2
DCO	Death certificate only
DS	Down syndrome
DNA	Deoxyribonucleic acid
EFS	Event-free survival
FAB	French-American-British Classification

FDA	Food and Drug Administration
FISH	Fluorescence *in situ* hybridization test
HL	Hodgkin lymphoma
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ICD-O-3	International Classification of Diseases for Oncology, 3rd edition
ICD-10	International Classification of Diseases, 10th revision
MDA	MD Anderson Cancer Center
MRC	Medical Research Council
MRD	Minimal residual disease
NAACCR	North American Association of Central Cancer Registries
NCI	National Cancer Institute
NDI	National Death Index
NHIA	NAACCR Hispanic Identification Algorithm
NAPIIA	NAACCR Asian/Pacific Islander Identification Algorithm
NOS	Not otherwise specified
NPCR	National Program for Cancer Registries
OR	Odds ratio
OS	Overall survival
PCR	Polymerase chain reaction
SEER	Surveillance, Epidemiology and End Results
SES	Socioeconomic status
SWOG	Southwest Oncology Group
UK	United Kingdom
US	United States

WBC	White blood cell
WHO	World Health Organisation

“The loss of a child in any culture or country, for whatever reason, is a societal tragedy.”

Professors Kathy Pritchard-Jones and Richard Sullivan[1]

Chapter 1 Introduction

1.1 Background

Acute leukaemia is the leading cause of cancer death among patients aged 39 or younger.[2, 3] Survival from acute leukaemia has improved dramatically over the last five decades, mainly due to intensive chemotherapeutic regimens, comprehensive supportive care and risk-adapted therapeutic regimens. Among children living in the United States (US) and Europe, 5-year overall survival after acute lymphoblastic (ALL) increased from less than 5% in the early 1960s[4] to 80%–90% at present.[5-7] Survival also increased substantially for children, adolescents and young adults with acute myeloid leukaemia (AML), mostly for specific subtypes of disease, such as acute promyelocytic leukaemia (APL) and core-binding factor (CBF) leukaemias.[8-10]

Survival among adolescents and young adults has been considerably lower than that observed for children with acute leukaemias.[10] One explanation for this may be that the biology of cancers affecting adolescents and young adults is markedly different than the biology of paediatric cancers, even when the malignancies appear clinically and histopathologically similar.[11] Another possibility is that adolescents and young adults have inferior participation in clinical trials than children, and this factor contributes to worse outcomes among these patients.[12]

Collaborative national and international clinical trials have played a key role in identifying more efficient and less toxic therapeutic regimens for patients from different age groups and subtypes of disease, and are considered the "gold standard" practice for the remarkable success of survival improvement after acute leukaemia.[13] Clinical trials commonly report relatively short

outcomes such as early death (death within 30 days after cancer diagnosis), event-free survival and 1- to 5-year overall survival. Overall survival has been long recognised as the most relevant clinical end point in clinical trials,[14] along with event-free survival. Event-free survival corresponds to the length of time that a patient remains free of complications or 'events' after cancer treatment. The event may be death, disease progression or severe drug toxicity.[15]

Despite their relevance, clinical trials, in general, provide data for less than 3% to 5% of the cancer population,[16] although this proportion is much higher among paediatric patients. For example, in the United Kingdom, during 1998–2002, 89% of children with cancer were referred to specialised cancer centres and treated on national protocols by the Children's Cancer and Leukaemia Group.[17] This proportion varies between and within countries, e.g., between 2000 and 2005, only about 40% of patients with acute lymphoblastic leukaemia aged 20 years or younger were enrolled in the Children's Oncology Group (COG) trials, which are mostly conducted in the United States and Canada.[12, 18] However, in these countries, children may be enrolled in clinical trials in other institutions, which use their own therapeutic protocols, such as Dana-Farber Cancer Institute and St. Jude Children's Research Hospital in the United States.

Whereas clinical trials usually select patients based on their risk stratification, performance status and comorbidities, population-based studies can provide information on virtually all patients with a specific cancer and therefore, are frequently representative of the entire population. Moreover, population-based studies can estimate both short-term (mentioned above) and

long-term outcomes (10 to 40 years or more), providing critical information on excess mortality after cancer treatment.

Despite substantial improvement over time, survival from acute leukaemia varies widely between and within countries.[5, 19] Survival is considered a fundamental measure of the effectiveness of health care systems, along with incidence and mortality trends.[20] In addition, the examination of early death (death occurring within 30 days of leukaemia diagnosis) is highly relevant for acute myeloid leukaemia, particularly for acute promyelocytic leukaemia, because patients with APL have an elevated risk of developing fatal haemorrhage, thrombosis and sepsis in the first days after diagnosis and induction of treatment.[21, 22] Epidemiological studies that investigate the factors associated with disease outcomes can reveal potential areas for improvement and help the development of health policies aimed at reducing childhood and young adult mortality after acute leukaemia. This is the main goal of my thesis.

1.2 Research aims

Using data from the State of California, my thesis had four main aims, described as follows.

The **first aim** was to perform a literature review on acute paediatric, adolescent and young adult leukaemia in order to identify the most important advances in disease outcomes and potential areas for improvement.

My **second aim** was to examine survival trends in children (0–14 years) and adolescents (15–19 years) diagnosed with acute lymphoblastic leukaemia during 1988–2011, and to investigate the association between survival and sociodemographic and selected clinical factors. These factors included age at

diagnosis, sex, race/ethnicity, health insurance status, type of treatment facility, and neighbourhood socioeconomic status (SES).

During my literature review, I learned that patients with acute promyelocytic leukaemia have a much better prognosis than patients with other subtypes of acute myeloid leukaemia, and therefore this entity should be studied separately. This directed me to my **third aim,** which was to evaluate survival and early death in children, adolescents and young adults (0–39 years) diagnosed with acute promyelocytic leukaemia during 1988–2011, and examine the association between survival and the sociodemographic factors and clinical factors mentioned in aim 2.

My **fourth aim** was to investigate survival and early death trends after acute myeloid leukaemia (excluding acute promyelocytic leukaemia) among patients aged 0–39 years during 1988–2011 and also examine factors associated with outcomes. This malignancy is more common in older adults but also occurs in younger patients, for whom there is a lack of population-based studies examining outcomes.[10]

The focus of this thesis was survival, but incidence rates and annual percentage change of acute leukaemias in California are also provided because of relevance, particularly to previous reports of increased incidence rates of certain types of leukaemias in the US[6, 23] and Europe over time.[24, 25] Leukaemia incidence is presented in this thesis for each subtype of disease, by race/ethnicity and over time, covering the studies' period of 1988–2011. Appendix 1 shows comparative charts of the distribution of each subtype of acute leukaemia by race/ethnicity in California.

1.3 Thesis structure

This is a research paper style thesis. The chapters have been structured as follows.

Chapter 2 provides information on the burden of paediatric and young adult acute leukaemia and presents an overview of the haematopoiesis and leukaemogenesis as well as leukaemia definition, classification, aetiology, risk stratification, diagnosis, treatment, and prognosis.

Chapter 3 provides a review of the literature, assessing how survival and, when appropriate, early death after acute leukaemia have changed in the last half-century, among paediatric and young adult patients.

Chapter 4 includes the Materials and Methods I used in this thesis. The first section gives detailed information on the data source and variables I have used. The second section describes the statistical methods I have applied and discusses some sources of bias that may occur when using population-based studies.

Chapters 5 to 7 contain three research papers, each introduced with a preamble, followed by the incidence data for each leukaemia subtype. **Chapter 5** provides information on how survival from acute lymphoblastic leukaemia varied over a 25-year period among children and adolescents in California. This study investigates the main factors associated with disease outcome and also provides descriptive information on leukaemia treatment (including chemotherapy and radiation), patient's cause of death, and secondary malignancies.

Chapter 6 contains the results of the evaluation of early death (7-day and 30-day mortality) among children, adolescents and young adults with

acute promyelocytic leukaemia before and after the introduction of all-*trans* retinoic acid (ATRA). This study looks at three calendar periods: the pre-ATRA era and the earlier and later ATRA eras. The cut point was the year 1995 when the US Food and Drug Administration (FDA) approved ATRA. This study also investigates survival after acute promyelocytic leukaemia and the main factors associated with disease outcomes. In addition, I present descriptive information on chemotherapy and cause of death.

Chapter 7 provides trends in early death and survival after acute myeloid leukaemia in children, adolescents and young adults in California over 25 years. This study also reveals the predictors of worse outcomes after acute myeloid leukaemia and provides descriptive information on treatment (chemotherapy and haematopoietic stem cell transplantation) and patient's cause of death.

Chapter 8 offers an overview of the thesis, the main findings, contribution of my work to the field of paediatric and young adult haematology and limitations. In this chapter I also provide information on my future research plans and present the concluding remarks.

1.4 Contribution of the candidate to the thesis

All research was performed as part of my PhD studies and took place during the period of my registration at the London School of Hygiene and Tropical Medicine (January 2013 to January 2016). Two papers have been published in, and one accepted by peer-reviewed journals based on the work undertaken for this thesis (Chapters 5, 6, and 7). I am the first and corresponding author of the three papers, carried out all the analyses, prepared all drafts, and

answered the reviewers' comments and suggestions. The co-authors' contributions to the manuscripts were limited to providing statistical advice and comments on the drafts that I had prepared, as well as on the responses to the reviewers, when applicable. The co-authors reviewed and approved the final version of my three papers, and also approved the three posters I have presented at national (United States) and international conferences. The papers were sent to scientific editors for proofreading before the submission to the journals. Each editor has been acknowledged in the corresponding paper.

The **first paper** was published in *Pediatric Blood and Cancer* in April (online) and October 2015 (printed). This work was presented at three conferences: World Cancer Congress in Melbourne, Australia in December 2014 (oral presentation); Global Cancer Research conference in Boston, United States in March 2015 (poster presentation); and GRELL Ascension meeting, Reus, Spain in May 2015 (poster presentation). I presented this work in Australia and in the United States, and my collaborator, Dr Rafael Marcos Gragera, presented it in Spain on my behalf.

The **second paper** was published in the journal *Cancer* in August (online) and November 2015 (printed version). I presented this study (poster) at the European Cancer Congress in Vienna, Austria, in September 2015.

The **third paper** was published in *British Journal of Haematology* in February (online) and April 2016 (printed). This work was presented (poster) in two conferences in the United States in December 2015: American Society of Haematology (ASH) annual meeting in Orlando-Florida and California Association of Regional Cancer Registries Conference (CARCR) in Sacramento-California. I presented the poster at ASH and my collaborator, Dr

Theresa Keegan, presented it on my behalf at the CARCR. The abstract was published in the Supplemental volume of *Blood* on 03 the December 2015.

The published versions of papers 1, 2 and 3 are provided in the Appendices 4, 5 and 6, respectively.

Chapter 2 Background

2.1 Haematopoiesis and leukaemogenesis

2.1.1 Normal haematopoiesis

Haematopoiesis relates to the production, proliferation, self-renewal, and differentiation of blood cells. In response to growth factors such as stem cell factor glycoproteins (Interleukins 1 to 7) and colony-stimulating factors, multipotent haematopoietic stem cells generate and maintain all differentiated lymphoid and myeloid cells present in the blood, bone marrow, spleen, and thymus.[26] The haematopoietic stem cells produce two progenitor cells: the common myeloid and common lymphoid cells. The common lymphoid progenitor cell originates the natural killer, T- and B-cells that are part of the immune system and have the key role of controlling infections.

The common myeloid progenitor cell generates three lineages of cells: erythrocyte, megakaryocyte, and myeloblast. The erythrocyte or red blood cell is responsible for carrying and delivering oxygen to the body organs and tissues. The megakaryocyte produces the platelets or thrombocytes, responsible for blood clotting. The myeloblast cell differentiates into four types of cells, which have the capability of defending the body against infection and toxins: neutrophils, eosinophils, basophils and monocytes. Figure 2.1 shows a schematic representation of human haematopoiesis.

2.1.2 Leukaemogenesis

Leukaemic transformation of a progenitor haematopoietic cell involves a disruption in the course of normal proliferation and differentiation process, resistance to apoptotic signals, and increased self-renewal. The prevalent

theory of leukaemogenesis is that a single haematopoietic cell suffers mutation and goes into an unlimited process of self-renewal resulting in malignant, poorly differentiated haematopoietic cells (clonal origin of leukaemic cell).[27]

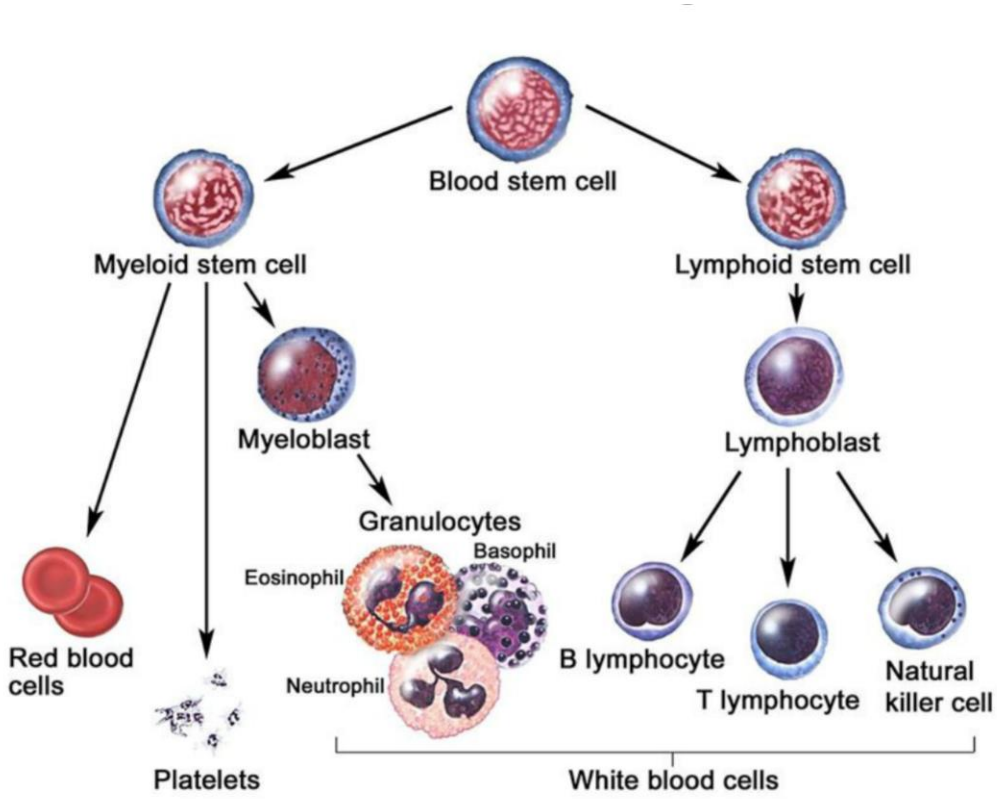

Figure 2.1: Haematopoiesis in humans. Source: Terese Winslow, 2008, US, http://www.cirm.ca.gov/files/files/about_stemcells/Unit_4_Appendix_B_0.pdf

Leukaemia cells behave differently than normal haematopoietic precursors, with slower cell division and longer time to produce DNA. Yet, these cells accumulate persistently in the bone marrow of leukaemic patients and progressively replace haematopoietic cells. Eventually, this process results in bone marrow failure, which is characterised by severe anaemia, bleeding, and infections.[27]

2.2 Disease definition

The word leukaemia derives from two Greek words: “leukos”, which means white, and “haima”, which means blood. Leukaemia is a malignancy of the blood and bone marrow characterized by uncontrolled proliferation of transformed haematopoietic cells, which have altered senescence and differentiation behaviour.[28]

Leukaemia can be characterised as acute or chronic. In acute leukaemia, the abnormal clonal proliferation contains very immature cells (blasts) that do not function properly. The blasts multiply quickly and the disease progresses rapidly. In chronic leukaemia, the blasts tend to proliferate more slowly than in acute leukaemia, the abnormal cells show various levels of differentiation beyond the blast stage, and may even function normally.

Acute lymphoblastic (also called lymphocytic or lymphoid) leukaemia is a malignant transformation of lymphoid progenitor cells and can be classified into B-cell and T-cell neoplasms. If the bone marrow and peripheral blood is extensively involved, lymphoblastic leukaemia is the appropriate term.[29] The term lymphoma is applied when the disease presents as a tumour with no or minimal evidence of bone marrow and peripheral blood involvement. Acute myeloid (also termed myelocytic, myelogenous, or non-lymphoblastic/lymphocytic leukaemia) is a very heterogeneous disease caused by malignant transformation of myeloid progenitor cells with various subtypes, described later in this Chapter and in Chapter 3.

2.3 Diagnosis and classification

2.3.1 Diagnosis of acute leukaemia

In the past, morphologic analysis was used to classify leukaemia in two categories: myeloid or lymphoid. Currently, advanced diagnostic techniques such as flow cytometry for immunophenotypic analysis, conventional and molecular genetics as well as next-generation sequencing-based multigene mutation profiling provide precise diagnosis and classification of leukaemias that are fundamental to guiding targeted therapy. Some tests are useful not only for diagnosis, but also to evaluate if therapy has been effective or modifications of the initial treatment is required. The common tests used to determine initial response to therapy include the fluorescence *in situ* hybridization (FISH) test, flow cytometry and polymerase chain reaction (PCR).[30]

The diagnosis of leukaemia can often be done by analysis of the peripheral blood. However, bone marrow examination is also required because up to 20% of patients may not present with blasts in the peripheral blood at the time of clinical presentation.[31] In addition, the morphology of leukaemia cells in the blood may differ from the cells in the bone marrow. The samples are commonly obtained by aspiration and, in selected cases, by biopsy of the bone marrow if necessary (e.g., when the marrow is extremely hypocellular or there is myelofibrosis).[32]

The peripheral blood frequently shows anaemia and thrombocytopenia with a decrease or increase of leucocytes and a predominance of blasts. In the bone marrow, the normal cells are replaced by variable amounts of blasts or abnormal promyelocytes (in the case of acute promyelocytic leukaemia). The

lineage of leukaemia (lymphoid or myeloid) is often established by morphologic and cytochemical examination and, in selected cases, by immunophenotypic analysis. After that, the percentage of blasts in the marrow is evaluated. For the diagnosis of acute lymphoblastic leukaemia, a marrow replacement of approximately 25% by lymphoblasts is generally used as an arbitrary cut-off. For acute myeloid leukaemia, the criteria for diagnosis vary according to the classification used. The more recent World Health Organisation (WHO) classification[29] requires 20% or more marrow replacement by myeloblasts, whereas the old French-American-British (FAB)[33] classification required 30% or more myeloblasts in the bone marrow.

Clinical features

The clinical features of acute leukaemia are secondary to the accumulation of malignant cells with consequent bone marrow failure. Symptoms may precede the clinical diagnosis by weeks or months and they are often non-specific. They include lethargy, pallor, easy or spontaneous bruising, fever, and infection. Bone pain and/or limping are very common symptoms. Physical examination may show lymphadenopathy, hepatomegaly and/or splenomegaly as well as weight loss.[27]

2.3.2 Classification of acute leukaemia

In addition to morphology, immunophenotypic, cytogenetic and molecular analyses are needed to better classify leukaemias into different subtypes, many of which require specific treatment approaches and have different prognostic implications. The WHO Classification of Tumours of Haematopoietic

and Lymphoid Tissues,[29] 4th edition, published in 2008, incorporates information on cell lineage, morphology, immunophenotype, and clinical and genetic characteristics. This manual has been recognised as the international standard classification system for leukaemia and other haematological diseases. The Haematopoietic and Lymphoid Neoplasm Coding Manual[34] of the Surveillance Epidemiology and End Results (SEER) Programme used in this thesis, is based on the 2008 WHO Classification.

2.3.2.1 Acute lymphoblastic leukaemia

Over the past 50 years, various classifications of diseases of lymphoid tissues and haematopoietic system have been recommended. Lymphoblastic leukaemias and lymphomas were believed to be distinct diseases and were classified separately. The WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 3rd Edition, published in 2001, classified malignant neoplasms into broad groups of haematologic lineage such as myeloid and lymphoid. In these broad groups, lymphoid tumours were called lymphomas when presented in their solid phase and leukaemias when presented in the circulating phase. The 2008 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 4th edition recognises that the difference between them is artificial and that lymphoblastic leukaemia and lymphoblastic lymphoma are, in fact, spectrum of the same disease. The leukaemic cells circulating in the peripheral blood can originate in lymph nodes or in the bone marrow. Lymphomas are solid masses in lymph nodes or organs containing lymphoid tissue (e.g. spleen or liver) and may, occasionally, have circulating tumour cells. Table 2.1 shows the SEER classification for Lymphoid Neoplasms.

Table 2.1: SEER classification of Lymphoid Neoplasms. Source: Hematopoietic and Lymphoid Neoplasm Coding Manual, 2015.[34]

ICD-O-3	WHO Preferred Histologic Term
9727/3	Blastic plasmacytoid dendritic cell neoplasm*
9728/3	Precursor B-cell lymphoblastic lymphoma**
9729/3	Precursor T-cell lymphoblastic lymphoma, not otherwise specified (NOS)**
9835/3	Precursor cell lymphoblastic leukaemia, NOS**
9836/3	Precursor B-cell lymphoblastic leukaemia**
9837/3	T lymphoblastic leukaemia/lymphoma*
9811/3	B lymphoblastic leukaemia/lymphoma, NOS***
9812/3	B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2*);* BCR-ABL1***
9813/3	B lymphoblastic leukaemia/lymphoma with t(v;11q23); *MLL* rearranged***
9814/3	B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22); *TEL-AML1 (ETV6-RUNX1)****
9815/3	B lymphoblastic leukaemia/lymphoma with hyperdiploidy***
9816/3	B lymphoblastic leukaemia/lymphoma with hypodiploidy***
9817/3	B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); *IL3-IGH****
9818/3	B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PBX1 (TCF3-PBX1)****
Based on the WHO 2001 classification: *codes effective from 2001 onwards, **codes valid for 2001–2009 only. Based on the WHO 2008 classification: ***codes valid from 2010 onwards.	

2.3.2.1 Acute myeloid leukaemia

The WHO classifies the myeloid neoplasms into five major groups including acute myeloid leukaemia. Using the tests diagnostics mentioned earlier in this section, acute myeloid leukaemia is subclassified according to its lineage into granulocytic, monocytic, erythroid or megakaryocytic. Using the 2008 WHO classification for Haematopoietic Tumours, acute myeloid leukaemia is also defined based on recurrent cytogenetic lesions, concurrent or pre-existing multilineage dysplasia, chemotherapy-related myeloid malignancy, and whether or not associated with Down syndrome.[32] SEER has been using the new classification with genetic information since 2010. These data will provide relevant information for future studies, but it will require several years until we

have sufficient number of patients to conduct robust incidence and survival analyses by subtype of acute myeloid leukaemia. Table 2.2 shows the SEER classification for Myeloid Neoplasms.

Table 2.2: SEER classification of Myeloid Neoplasms. Source: Hematopoietic and Lymphoid Neoplasm Coding Manual, 2015.[34]

ICD-O-3	WHO Preferred Histologic Term
Acute myeloid leukaemias with recurrent genetic abnormalities	
9911/3	Acute myeloid leukaemia (megakaryoblastic) with t(1;22)(p13;q13*); RBM15-MKL1*
9869/3	Acute myeloid leukaemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
9871/3	Acute myeloid leukaemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
9865/3	Acute myeloid leukaemia with t(6;9)(p23;q34); *DEK-NUP214*
9896/3	Acute myeloid leukaemia with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
9897/3	Acute myeloid leukaemia with t(9;11)(p22;q23); *MLLT3-MLL*
9866/3	Acute promyelocytic leukaemia with t(15;17)(q22;q12); PML-RARA
9895/3	**Acute myeloid leukaemia with myelodysplasia-related changes**
9920/3	**Therapy-related myeloid neoplasm**
9861/3	Acute myeloid leukaemia, NOS
9870/3	Acute basophilic leukaemia
9840/3:	Acute erythroid leukaemia
9910/3	Acute megakaryoblastic leukaemia
9891/3	Acute monoblastic and monocytic leukaemia
9874/3	Acute myeloid leukaemia with maturation
9872/3	Acute myeloid leukaemia with minimal differentiation
9873/3	Acute myeloid leukaemia without maturation
9867/3	Acute myelomonocytic leukaemia
9931/3:	Acute panmyelosis with myelofibrosis
9898/3	**Myeloid leukaemia associated with Down Syndrome**

2.4 Epidemiology and aetiology

2.4.1 Incidence

Childhood cancer is a rare disease accounting for less than 2% of the global cancer burden. Yet, every year more than 160,000 children are diagnosed with cancer worldwide.[35] With current population growth and decrease in childhood mortality rates (mostly due to lower mortality from infectious diseases), the incidence of childhood cancer is expected to increase by 30% by 2020.[36] About 70% of new cases are predicted to occur in low- and middle-income countries, where more than 80% of paediatric cancer deaths currently occur.[37]

Leukaemia is the most common type of childhood malignancy, representing a third of all paediatric cancers and about 10% of malignancies in adolescents in the developed world. Acute lymphoblastic leukaemia accounts for approximately 75%–80% of all childhood leukaemias with an annual incidence rate of approximately 4/100,000 persons per year in the United States and Europe.[24, 35]

There is significant geographical variation in the incidence of childhood leukaemia. Childhood acute lymphoblastic leukaemia incidence varies from 1 to 4.95/100,000 persons per year, with the highest rates reported in Mexico,[38] Costa Rica[39] and among whites and Hispanic children living in the United States.[40, 41] Incidence is also high in Australia and Germany with intermediate rates in most European countries. Incidence of acute lymphoblastic leukaemia is lower in the Middle East, Sub-Saharan Africa, India, and among black children in the United States.[32] It is unclear how much geographic variation is due to environmental or genetic factors, or under-diagnosis of common acute lymphoblastic leukaemia in some countries.[42] A previous study measured

completeness of cancer registration in Kampala, Uganda among patients aged 15 years or older. Overall, completeness of ascertainment was 89.6% and varied by age (better for younger patients) and tumour site.[43]

The incidence rates of childhood acute lymphoblastic leukaemia have increased significantly since 1970s, by 1.4% per year in Europe[25, 44] and 0.5%–0.8% in the United States,[6, 23] but have remained stable in the Nordic countries.[45] Figure 2.2 shows the distribution of acute lymphoblastic leukaemia by age group in the United States using SEER data. SEER 18 includes data available for all cases of cancer diagnosed from 2000 onwards in the following cancer registries: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San-Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska, Greater California, Kentucky, Louisiana (adjustments were needed for cases occurred during July to December in 2005 due to Hurricanes Katrina and Rita), New Jersey, and Greater Georgia.[46]

Almost universally, the age-adjusted incidence for boys exceeds that for girls, with the sex ratio for acute lymphoblastic leukaemia typically between 1.2 to 1.[47] In the developed countries, white patients have moderately higher rates of leukaemia than non-white patients.[48] For instance, in the United States, the annual incidence rates of acute lymphoblastic leukaemia in white children are about twice those in black children. Age-specific incidence of acute lymphoblastic leukaemia presents a characteristic peak at 2–5 years for the common acute lymphoblastic leukaemia in most industrialised countries. This early peak is less marked or even absent in economically disadvantaged populations (including black patients in the United States and various low- and

middle-income countries), and this is precisely the age range with the best prognosis for acute lymphoblastic leukaemia.[42, 44, 49]

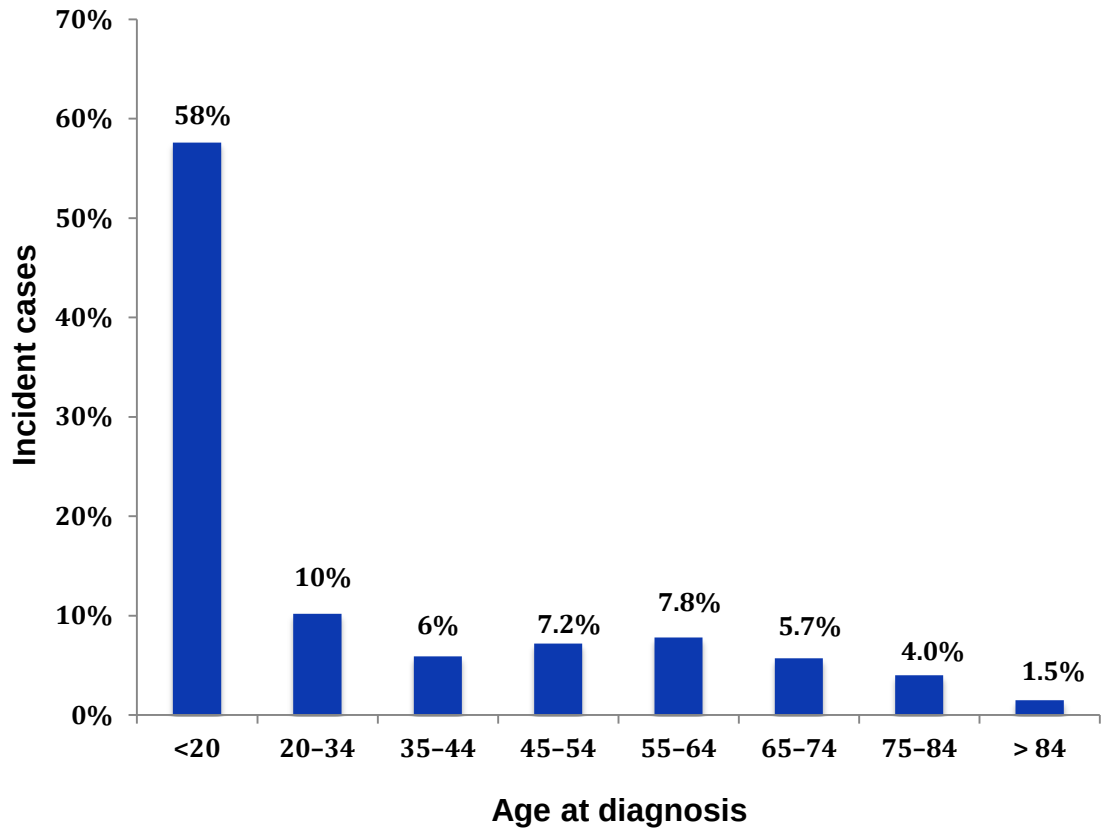

Figure 2.2: Percentage of new cases of acute lymphoblastic leukaemia by age groups in the United States, SEER18, 2008–2012, all races, and both sexes. Adapted from NCI SEER Stat Fact Sheets: Acute Lymphocytic Leukaemia (ALL), 2015. http://seer.cancer.gov/statfacts/html/alyl.html[50]

Acute myeloid leukaemia comprises about 15%–20% of all paediatric leukaemias, with an annual incidence rate of 0.8/100,000 persons per year in the United States. Of those diagnosed with this malignancy, approximately 33% are adolescents and 50% are adults in the developed countries.[51] There is also substantial geographical variation in the incidence of acute myeloid leukaemia, with the highest incidence rates reported in China, Japan and among the Maori population in New Zealand. Intermediate rates are reported

in Australia, United Kingdom and in the United States. The lowest incidence rates of acute myeloid leukaemia are reported in India, Kuwait and Canada.[32]

Although acute myeloid leukaemia is a neoplasm more frequent in older people, this disease can occur at any age and remains the leading cause of cancer deaths among patients aged ≤ 39 years.[3] In contrast to acute lymphoblastic leukaemia, there is no evidence of a significant increase of incidence of acute myeloid leukaemia among children, adolescents and young adults in the United States[52] and Europe[53] over the last few decades. Figure 2.3 shows the distribution of acute myeloid leukaemia, by age group in the United States using more recent SEER data (2008–2012). Regarding race/ethnicity, Hispanic children have the highest incidence rates of acute myeloid leukaemia, mostly due to the high incidence of acute promyelocytic leukaemia in this population, suggesting genetic predisposition and/or exposure to environmental factors.[32]

2.4.2 Aetiology

Since its recognition in 1845, the search for an etiologic agent for leukaemia has been intense, and numerous factors have been proposed, from infectious, chemical or physical agents to genetic factors. To date, the precise pathogenic events that contribute to the development of leukaemia remain largely unknown, but it does appear that various factors may act together. Additionally, variations may exist from individual to individual and between different types of leukaemia.[54]

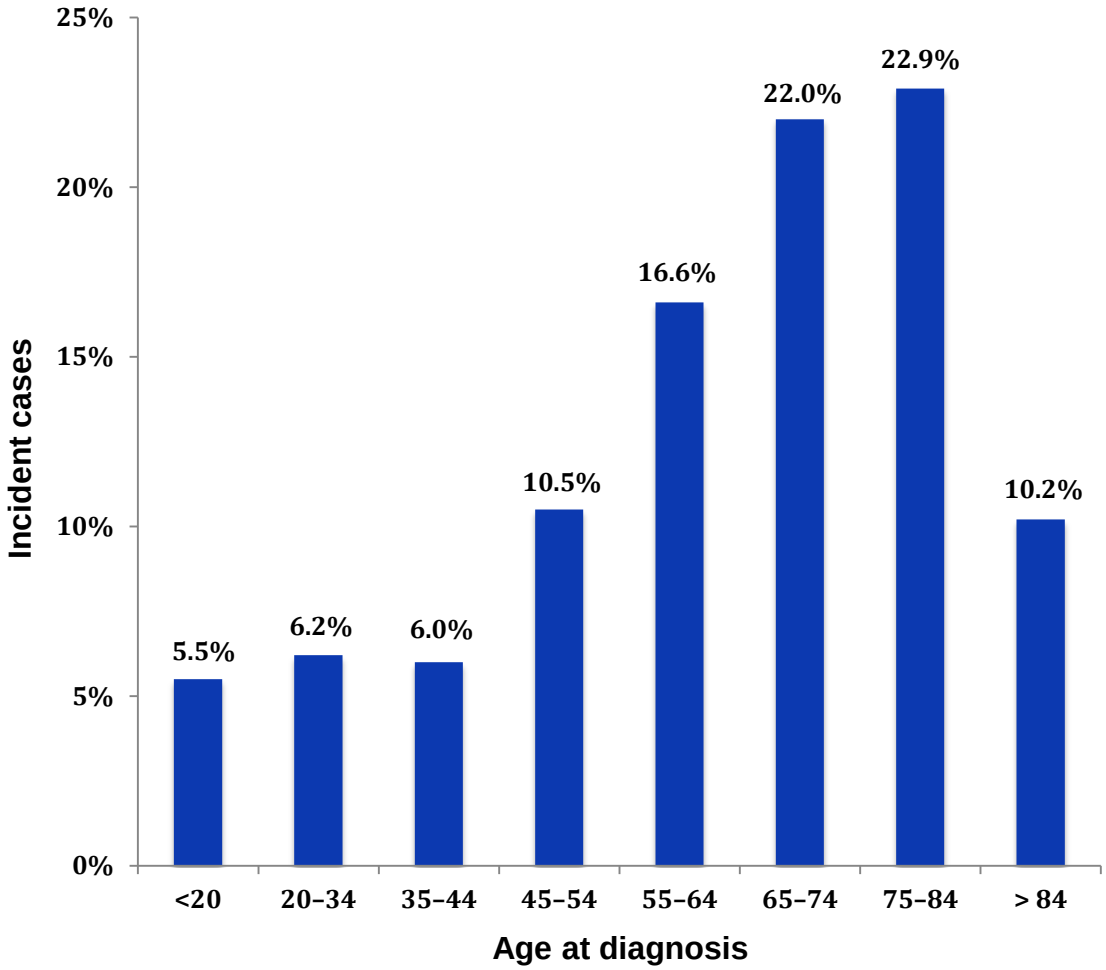

Figure 2.3: Percentage of new cases of acute myeloid leukaemia by age groups in the United States, SEER 18, 2008–2012, all races, both sexes. Adapted from NCI SEER Stat Fact Sheets: Acute Myeloid Leukaemia (AML), 2015.
http://seer.cancer.gov/statfacts/html/amyl.html [55]

Most of the environmental exposures that have been suggested lack biological or consistent epidemiological evidence. Ionizing radiation is the only established causal exposure for paediatric leukaemia.[56, 57] Less than 5% of incident cases are associated with inherited predisposing genetic disorders, such as Down and Li-Fraumeni syndromes, ataxia-telangiectasia, neurofibromatosis, polymorphism of xenobiotic metabolizing enzymes, or with prenatal exposure to X-rays or chemotherapeutic drugs.[58, 59] Children with

Down syndrome have a 10–20 fold increased risk of developing acute lymphoblastic or myeloid leukaemia than children without Down syndrome.[60]

Biological studies suggest that both prenatal and postnatal events may be involved in the development of leukaemia. Most chromosome translocations happen *in utero*, during foetal haemopoiesis, probably as initiating events. In most cases, secondary genetic events are also required. The most well-known hypotheses for the aetiology of childhood leukaemias are Kinlen's population-mixing[61] and Greaves' delayed infection hypotheses[62] described below and illustrated in Figure 2.4.*[58]*

Kinlen's hypothesis

Kinlen proposed that clusters of childhood acute lymphoblastic leukaemia result from a limited epidemic caused by a common but relatively non-pathogenic infection occurring in individuals who were susceptible, following contact or 'population mixing' with individuals who are infected. [61]

Greaves' hypothesis

Greaves suggested that both acute lymphoblastic and myeloid leukaemias in children originate from two spontaneous mutations. One would occur *in utero* through the generation of a pre-leukaemic clone caused by chromosomal rearrangements, a second is assumed to occur after birth, following the infant's first contact with a diverse range of antigens leading to secondary genetic abnormalities.[62]

Some studies suggest other risk factors for acute lymphoblastic leukaemia, but they are still controversial. They include the following: high

birthweight,[63-65] maternal reproductive history,[65] parental use of tobacco[66] or alcohol,[67] maternal diet,[68] parental exposure to pesticides[69] or paint and petroleum solvents,[70] and exposure to high levels (>0.3 or 0.4 μT) of residential power-frequency magnetic fields.[71]

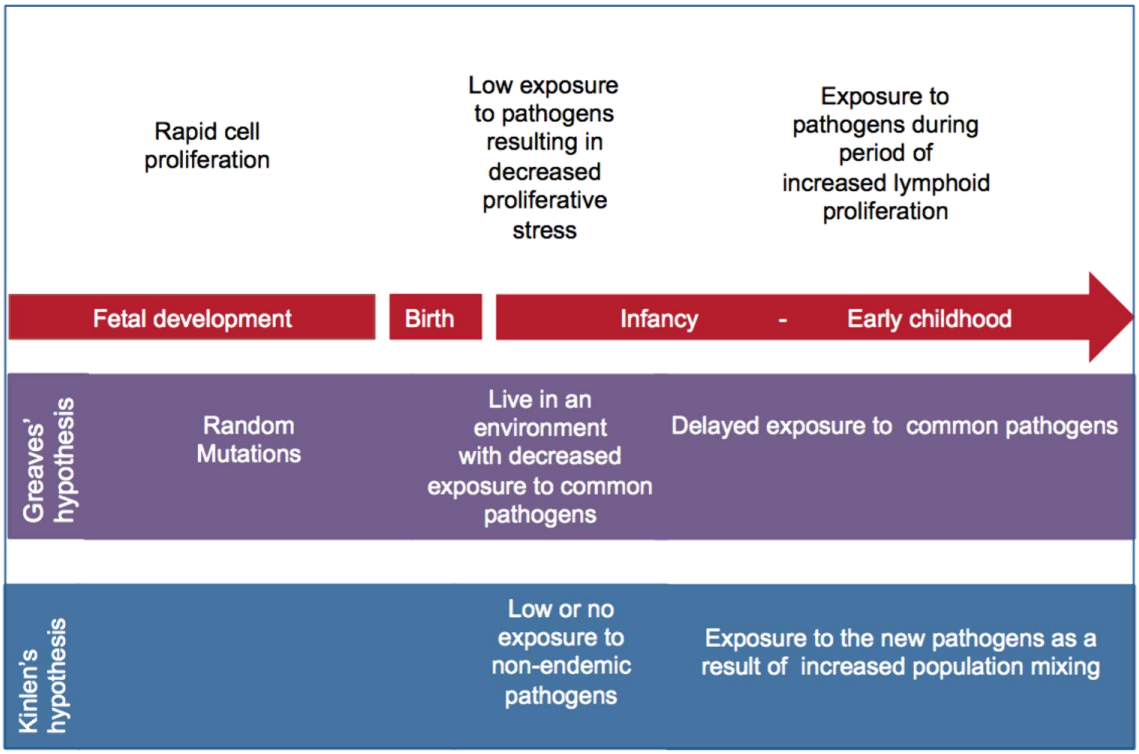

Figure 2.4: Infection-based models of leukaemia development. Adapted from Pui et al., *The Lancet* 2008[58]

Chromosomal translocations are often associated with acute leukaemia and it is well established that most of these patients carry multiple genetic abnormalities. Disease outcome varies not only among cytogenetic subtypes of leukaemia, but also within each subtype of disease. Patients carrying a single genetic alteration may have different associated genetic abnormalities[54] Genome-wide analyses of gene expression have helped the understanding of leukaemogenesis and prognosis, but little is known about how genetic mutations produce overt leukaemia or induce resistance to drugs used to treat

this disease. There is evidence that leukaemia with different biologic subtypes may not share the same causal associations. For instance, acute lymphoblastic leukaemia in infants is commonly associated with *MLL* gene rearrangements and has almost 100% concordance rate in identical twins. This suggests that the leukaemogenesis in this subtype of leukaemia is basically complete *in utero.* Distinctively, non-MLL rearrangement B-cell lymphoblastic leukaemia, which has a higher incidence in children aged 2–5 years, has a much lower concordance rate in identical twins (10%–15%).[72] This suggests that after an *in-utero* initiation process, a post-birth event may occur and lead to overt leukaemia.[73]

Figure 2.5 shows the multiple genetic events that can occur in the pathogenesis of B-cell lymphoblastic leukaemia at both diagnosis and relapse. For example, a haematopoietic stem cell lymphoid progenitor can have an initiation mutation that deregulates the normal haematopoiesis and may be influenced by inherited variants. This haematopoietic stem cell may progress to a mature B-cell (normal cell) or, through cooperative alterations undergo lymphoid leukaemogenesis. After chemotherapy, the leukaemic cells are destroyed and the patient is cured. However, on some occasions, one single resistant cell can be selected, undergo self-renewal and cause disease relapse. Genetic alterations that predispose to treatment resistance may be acquired or be present since diagnosis.

Currently, almost all patients with acute lymphoblastic leukaemia can be classified based on a specific genetic lesion. The most frequent genetic abnormalities in common acute lymphoblastic leukaemia are hyperdiploidy and

TEL-AML1 (ETV6-RUNX1) fusions. The frequency of specific genotypes in childhood acute lymphoblastic leukaemia is shown in Figure 2.6.[72]

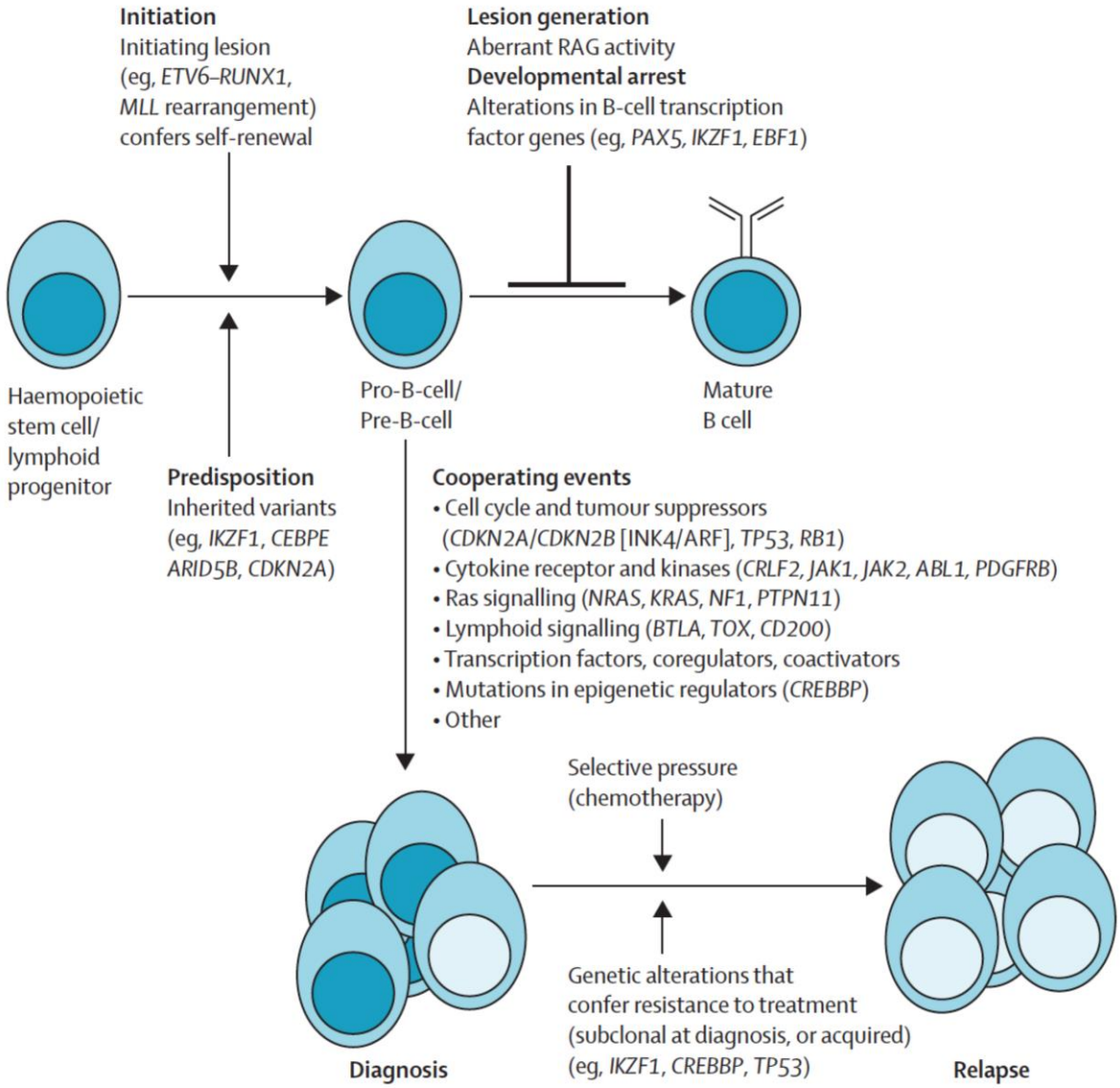

Figure 2.5: Multiple genetic events in acute lymphoblastic leukaemia at diagnosis and relapse. Source: Inaba et al., *The Lancet* 2013[73]

Adolescents and young adults with acute lymphoblastic leukaemia often have inferior outcomes compared to children with this disease. This fact is partially explained by the increased frequency of Philadelphia chromosome

positive and T-cell ALL associated with inferior outcome in the older population. Moreover, there is a lower incidence of *ETV6-RUNX1* fusion and hyperdiploidy among adolescents and young adults, alterations that are associated with better outcome.[58, 72, 74]

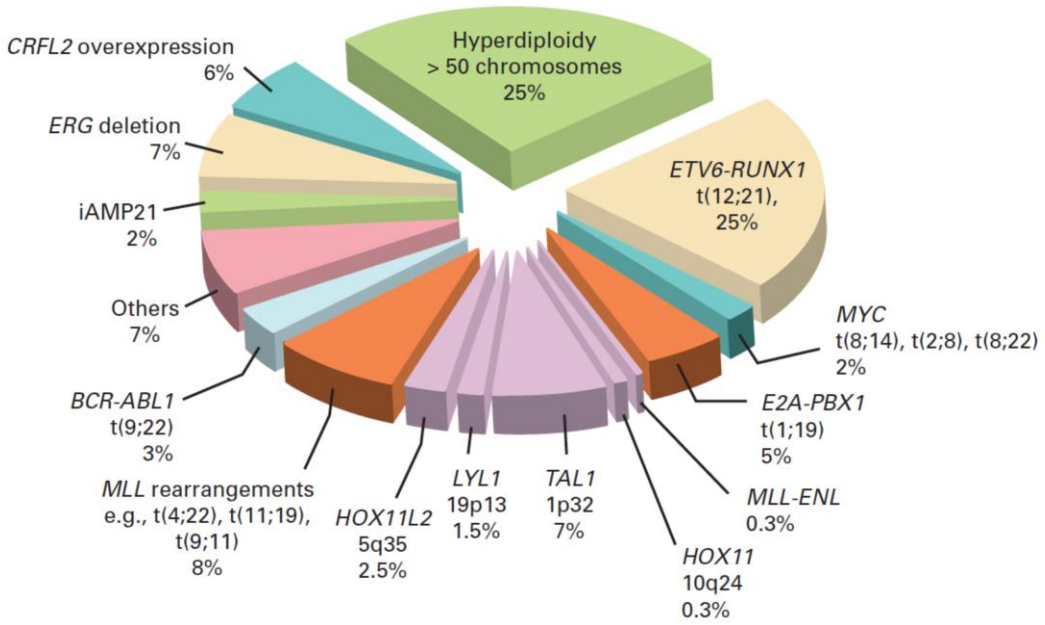

Figure 2.6: Genomic abnormalities in childhood acute lymphoblastic leukaemia. The genetic alterations seen exclusively in patients with T-cell ALL are shown in purple. Source: Pui et al., *J Clin Oncol* 2011[72, 75]

Acute myeloid leukaemia is a complex and very heterogeneous malignancy. However, there is enough evidence that acute myeloid leukaemia subtypes share a few similar pathways that results in leukaemogenesis and overt disease.[76] The accepted hypothesis is that acute myeloid leukaemia is a consequence of two collaborative types of genetic alterations that controls cell self-renewal and differentiation.[77] Figure 2.7 shows the most frequent genetic alterations in children with acute myeloid leukaemia. Approximately 95% of children with acute myeloid leukaemia have at least one genetic alteration.

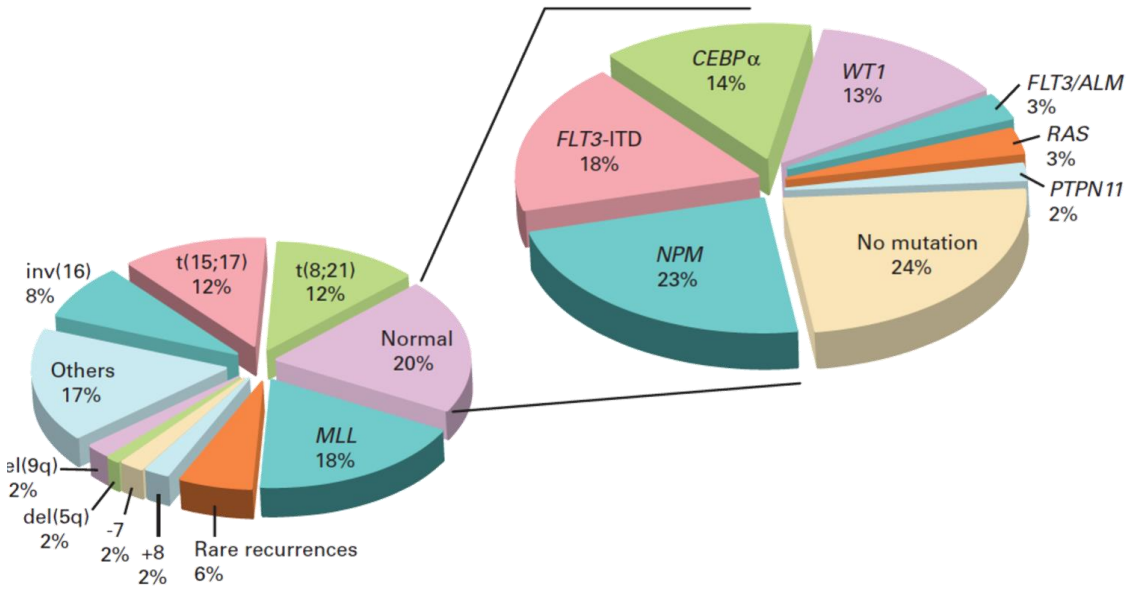

Figure 2.7: Genetic abnormalities in childhood acute myeloid leukaemia. Left side: most common karyotypic alterations. About 80% of all children with AML have genomic structural alterations. Right side: mutation profile in children with AML with normal karyotype. Source: Pui et al., *J Clin Oncol* 2010[72, 75]

2.5 Risk stratification, treatment and prognosis

The recognition that acute lymphoblastic and myeloid leukaemias are heterogeneous disease has guided risk-directed therapy aimed at improving survival as well as the quality of life of survivors.[58] The identification of patients with high risk of relapse allows that very intensive treatment is provided only for high-risk patients, hence preventing excessive toxic effects among cases with low-risk disease.[78] Cytogenetic and molecular characteristics as well as assessment of minimal residual disease have been substituting many conventional prognostic factors in both acute lymphoblastic and myeloid leukaemias. The risk stratification of acute leukaemias and several risk adapted-treatments are described in the sections below.[72]

2.5.1 Acute lymphoblastic leukaemia

Specific treatment approaches for acute lymphoblastic leukaemia may differ depending on the disease presentation, but they regularly include remission-induction, intensification or consolidation treatment, and maintenance therapy to eradicate leukaemia cells.[27]

Patients with acute lymphoblastic leukaemia generally need long maintenance treatment in order to prevent relapse. During 6 to 12 months, intensive multidrug chemotherapy is used, followed by a less intensive regimen for 2.5 to 3 years, given daily or weekly. The mechanism by which lower dose chemotherapy regimen eradicates the residual leukaemic cells is poorly understood.

When continuation treatment was given during a shorter period of time (18 months or less) for children and adults with acute lymphoblastic leukaemia, survival was lower than that of conventional treatment. While approximately 65% of young patients may be cured with only 12 months of chemotherapy, it is not possible to identify these cases with certainty and the current recommendation is to treat these patients for two years or more.[27] Common drugs used for the treatment of acute lymphoblastic leukaemia include corticosteroids, asparaginase and vincristine.[79]

Currently, early response to therapy is assessed by most groups via measurement of residual disease at specific time points in treatment: at day 8 in the peripheral blood and day 29 in the bone marrow.[25] Minimal residual disease, which is the number of residual leukaemia cells expressed in percentage of normal nucleated cells in the bone marrow, has been recognised as the most important prognostic factor for survival in patients with

acute lymphoblastic leukaemia and can be detected by polymerase chain reaction or by flow cytometry. One study lead by the Children's Oncology Group,[30] revealed that the presence of minimal residual disease in the blood at day-8 and in the bone marrow at day-29 was associated with lower event-free survival (length of time after cancer treatment that the patient remains free of disease or complications). This occurred in all patients diagnosed with B-ALL regardless risk group stratification. Even children with as little minimal residual disease as 0.01% to 0.1% leukaemia cells at day 29 had worse event-free survival than patients negative for minimal residual disease (5-year EFS was 59% vs. 88%, respectively). This suggests that continuous minimal residual disease monitoring may be useful to identify patients with high or intermediate risk of relapse (those with a somewhat slow early response to therapy) and guide therapy. However, clinicians should be aware that some patients with persistent minimal residual disease may be cured, while some patients with minimal residual disease negative (undetectable) at remission can still present leukaemia recurrence.[80, 81] This emphasises the fundamental role of maintenance treatment for patients with acute lymphoblastic leukaemia.

Treatment directed at the central nervous system is of key importance and should be initiated early in the course of treatment. Several factors are taken into account when selecting the intensity of therapy, such as risk of relapse and the quantity of leukaemic cells in the cerebral spinal fluid.[82] It has been established that cranial irradiation can cause various acute and late adverse effects such as secondary malignancies, neurocognitive disorders and endocrinopathies. Consequently, in many centres, cranial irradiation has been replaced by intrathecal and systemic chemotherapy.[83, 84 82]

Induction failure is rare in children, and can be defined as the presence of leukaemic cells in the peripheral blood, bone marrow or extra medullary location after 4–6 weeks of induction therapy. All children with acute lymphoblastic leukaemia who have induction failure are considered very high-risk patients and haematopoietic stem-cell transplantation is recommended.[85] In a previous study, children who had T-cell leukaemia appeared to have higher survival with transplantation than with chemotherapy, while children who had precursor B-cell leukaemia without other unfavourable characteristics appeared to have higher survival with chemotherapy alone.[86]

Detailed information on adolescents and young adults is comparatively scarce because of the smaller number of incident cases in this age group, as well as lower enrolment of these patients in clinical trials compared with children and older adults.[87] Consequently, adolescents are commonly examined together with children aged 10–15 years in paediatric trials or with patients aged 20–30 years in adult trials.[74] There is evidence that substantial decline in survival is observed beyond 15 years of age at diagnosis.[88]

One study examined patients aged 16–20 years with acute lymphoblastic leukaemia enrolled in the Children's Cancer Group (CCG) and Cancer and Leukaemia Group B (CALGB) clinical trials, and compared outcomes from the distinct protocols used by these groups. Sever-year event-free survival and overall survival were 63% and 67% respectively for patients treated on CCG protocols vs. 34% and 46% for those treated on CALBG protocols. The main differences between both treatment approaches were earlier and more intensive central nervous system prophylaxis and higher

cumulative doses of nonmyelosuppressive drugs used by CCG compared to CALBG protocols.[74]

At present, evidence suggests that intensified treatment protocols may reduce or eliminate the influence of some prognostic factors, such as male sex, black race and Down syndrome, on survival.[89, 90] One study in the United States showed that when intensified treatment is provided, black and white children of both sexes have the same chance of attaining high survival and cure.[90] However, these results need to be interpreted with caution because, to date, they have only been observed in a single institution. Moreover, although children with Down syndrome have an increased risk of developing acute lymphoblastic leukaemia and lower survival, outcomes are comparable in children with and without Down syndrome after adjustment for favourable and unfavourable cytogenetic lesions.[91]

Clinical trials have identified several factors predictive of outcomes after acute lymphoblastic leukaemia, as summarised in Table 2.3.[92] The few particular subgroups of high-risk patients with acute lymphoblastic leukaemia that should be treated with a risk-adapted protocol are described below.[72]

Philadelphia Chromosome-Positive ALL

Due to the extremely poor prognosis in the past, children Philadelphia Chromosome-Positive ALL are currently treated with intensive chemotherapy plus imatininb or desatinib, tyrosine kinase inhibitors. Haematopoietic stem cell transplantation may be recommended in case of relapse.

High-Risk T-cell ALL

The management of patients with high-risk T-cell ALL requires intensive treatment with asparaginase and dexamethasone. A subtype of T-cell ALL called early T-cell precursor ALL has a dismal prognosis even when they undergo haematopoietic stem cell transplantation. Clinicians and researchers continue to explore new treatment strategies aimed at improving outcomes of patients with this entity.

Infant acute lymphoblastic leukaemia

Infants with acute lymphoblastic leukaemia continue to fare poorly even with intensive therapeutic regimens. The role of haematopoietic stem cell transplantation in first remission has been investigated in very high-risk patients (age <6 months, WBC > 300 X $10^{9,}$ and MLL rearrangement).[72]

Table 2.3: Predictors of outcome and treatment response for children with acute lymphoblastic leukaemia. Adapted from Hunger et al., *Pediatr Blood Cancer 2013.*[92]

	Good prognosis	Poor prognosis
Age at diagnosis	> 1 and < 10 years	<1 or ≥ 10 years
WBC count at diagnosis	< 50,000/μL	≥ 50,000/μL
Immunophenotype	B-precursor ALL	T-precursor ALL
CNS or testicular leukaemia	Absent	Present
Presence of genetic lesions	*ETV6-RUNX1* fusion Hyperdiploidy with favourable chromosome trisomies	MLL-rearrangements (MLL-R) Hypodiploidy (<44 chromosomes) Intrachromosomal amplification of chromosome 21 (iAMP21) Philadelphia chromosome positive: t(9;22) BCR/ABL
Early treatment response	Yes	No
MRD after induction	<0.01%	≥ 1%
Abbreviations: ALL, acute lymphoblastic leukaemia; CNS, central nervous system; WBC, white blood cell		

Adolescent and young adult acute lymphoblastic leukaemia

As mentioned in section 2.5.1, adolescent and young adults with acute lymphoblastic leukaemia have poorer outcomes compared with children. In the mid-2000s, collaborative trials began to treat these patients with paediatric protocols and several studies have shown excellent results.[93-95] Between 2007 and 2012, a large prospective adult intergroup trial (C10403)[96] in the United States, investigated the adoption of a successful protocol used by the Children's Oncology Group (COG ALL0232) for treatment of patients aged 16–39 years with acute lymphoblastic leukaemia.[97] A total of 296 patients with B- or T-cell ALL were treated with paediatric protocols by adult haematologists/oncologists. The significant improvement in outcomes (event-free survival and overall survival) supports the use of paediatric protocols by adult haematologists to treat adolescents and young adults with this neoplasm. However, despite of improvement, there is evidence that these patients continue to be treated with low-intensity chemotherapy regimens in many centres.[98] An explanation may be that some clinicians are not yet convinced about the paediatric approach superiority compared to the conventional treatment and may await more evidence from a randomized Phase III study.[98] Another possibility is that adult haematologists might not feel as familiar as paediatricians in managing the treatment-related toxicity secondary to the intensive paediatric protocol. Some complications of treatment such as pancreatitis, osteonecrosis, hyperglycemia, and infection seem to occur more often in older patients (> 10 years old). This may cause adult clinicians to change prescribed drug dosage and schedule.[99, 100] Lastly, while most

academic centres in the United States have adopted the paediatric regimens this may not be the same in community hospitals.[98]

In spite of the dramatic improvement in survival, an appreciable risk of death remains for many years after diagnosis of acute lymphoblastic leukaemia, and significant numbers of children and adolescents still die of relapsed or refractory disease. The main determinants of survival are time to relapse, site of relapse, leukaemia immunophenotype, and more recently, minimal residual disease. Patients who present relapse within 36 months of diagnosis have a dismal 5-year overall survival of approximately 15%.[92, 101]

Salvage chemotherapy or even haematopoietic stem cell transplantation for both adults and children with relapsed or refractory acute lymphoblastic leukaemia have not improved outcome, and intensive research continues to be done in order to find new therapeutic agents able to improve survival in these patients. New monoclonal antibodies such as cluster of differentiation (CD) 19, CD20, CD22, and CD52 have been developed. The rationale for the use of monoclonal antibodies is that lymphoblasts express various cell-surface antigens that may be favourable targets for this therapy. For instance, over 95% of B-cell ALL and more than 90% of lymphoblasts express CD19 and CD22, respectively.[102] Monoclonal antibody therapy has been recently used in clinical trials to treat children and adults with relapsed or refractory acute lymphoblastic leukaemia. The initial results have been favourable with good tolerability and high levels of negative minimal residual disease. However, longer follow-up time is necessary to assess toxicity and long-term outcome. [102]

2.5.2 Acute myeloid leukaemia

Similar to acute lymphoblastic leukaemia, risk-adapted therapy has become critical for acute myeloid leukaemia. Acute myeloid leukaemia has been risk stratified in two major groups. The low risk group (about 25% of the cases) includes patients with CBF AML (t[8;21], inv16, t[15;17]), infant AML, AML with Down syndrome, AML with *CEBPA* and *NPM*1 mutations (non-*FLT3-ITD) or* megakaryoblastic AML with the t(1;22) abnormality, and minimal residual disease negative. The high-risk group (about 25% of the cases) includes patients with unfavourable cytogenetic alterations (monosomies 5 and 7), *FLT3-ITD and TP53* mutations*,* secondary AML, AML associated with myelodisplastic syndrome, and minimal residual disease positive.[72] In approximately 40%–50% of cases there is not a good genetic or molecular marker to determine the disease prognosis and clinicians use minimal residual disease assessment to guide treatment.[103]

In general, the treatment of acute myeloid leukaemia is performed using four to five intensive courses of cytarabine and anthracyclines chemotherapy. Maintenance therapy appears not to have any advantage in acute myeloid leukaemia as it occurs for acute lymphoblastic leukaemia. Central nervous system directed therapy with triple agents is also recommended for acute myeloid leukaemia. Haematopoietic stem cell transplantation is performed more often among young patients with acute myeloid leukaemia than for acute lymphoblastic leukaemia (about 30% vs. 5%).[72]

Core-binding factor AML

Core-binding factor AML (CBF AML) is associated with chromosomal rearrangements between chromosomes 8 and 21 (t8;21) and within chromosome 16 (inv [16]). This subtype accounts for about 25% of all childhood acute myeloid leukaemia cases and its prevalence decreases with advancing age. CBF AML prevalence is approximately 10%–15% in adults aged 60 years or younger and 5% in patients older than 60 years.[104] With intensive chemotherapy regimens with three to four drugs, CBF AML has become a group of good prognosis with 3-year overall survival of approximately 90% in children and adolescents[105] and about 69% for young adults.[8] Patients with t(8;21) AML may have a higher incidence of relapse than those with inv(16). However with the receipt of haematopoietic stem cell transplantation, they have a high possibility of cure.[72]

Children and young adults with acute promyelocytic leukaemia have also a favourable prognosis with 3-year overall survival of approximately 75%–90% when all-*trans* retinoic acid or arsenic trioxide is associated to conventional chemotherapy.[106] Haematopoietic stem cell transplantation is not recommended for children in complete remission, but may be indicated for those who relapse.[72]

Down syndrome and acute myeloid leukaemia

In contrast to acute lymphoblastic leukaemia, patients with acute myeloid leukaemia and Down syndrome have a better prognosis than non-Down syndrome patients with acute myeloid leukaemia. Therefore, the current

treatment approach is to reduce chemotherapy agents in order to avoid complications of treatment, particularly cardiotoxicity.

Neonatal and infant acute myeloid leukaemia

Because neonates with acute myeloid leukaemia may have spontaneous remission, some clinicians may choose to observe them rather than begin chemotherapy immediately. When chemotherapy is necessary, careful dose adjustments should be done in order to avoid toxicity. Neonates tend to have worse clinical course due to complications of treatment and disease resistance than children. On the contrary, infants with acute myeloid leukaemia often have similar prognosis as older children provided that they receive intensive chemotherapy regimen. Haematopoietic stem cell transplantation seems not to improve outcome in these patients and can cause serious adverse effects.

Acute myeloid leukaemia with altered genes (*FLT3-ITD*, *NPM* and *CEBPA* mutations)

FLT3-ITD mutations are associated with poor prognosis in children (5-year overall survival < 35%).[107] The use of haematopoietic stem cell transplantation is still controversial, being usually reserved for high-risk patients. In contrast, patients with *FTL3* point mutation have a better outcome and are often treated with chemotherapy only. Patients with *NPM* and *CEBPA* mutations have a favourable prognosis; therefore haematopoietic stem cell transplantation is not usually recommended for these patients.

AML with MLL-rearrangements

AML with MLL-rearrangements is a heterogeneous disease and prognosis may vary from 22% for patients with t(6;11) to 100% for those with t(1;11). The role of haematopoietic stem cell transplantation remains controversial in this subtype of disease.[108]

In summary, the prognosis of acute leukaemia has improved substantially in the last few decades, mainly for acute lymphoblastic leukaemia and some subtypes of acute myeloid leukaemia. This improvement was possible due to national and international collaborative clinical trials that investigate the association of various factors on outcome. Risk-adapted therapy based on patient' clinical and genetic features and minimal residual disease assessment have largely contributed to treatment success in both acute lymphoblastic and myeloid leukaemia treatments. However, for specific types of disease, prognosis is still poor and new treatment approaches are warranted.

Chapter 3: Literature review

This literature review was divided in two sections. The first section contains the literature review on acute lymphoblastic leukaemia (ALL) and the second section provides the literature review on acute myeloid leukaemia (AML). The second section was subdivided in order to study acute promyelocytic leukaemia (APL) and acute myeloid leukaemia (non-APL) separately.

3.1 Acute lymphoblastic leukaemia

3.1.1 Aims

The main aim of this literature review was to identify how survival from childhood acute lymphoblastic leukaemia varied over time in different populations, and to document the main advances in the diagnosis and treatment of this malignancy. I have also investigated, as a secondary aim, worldwide trends in incidence of acute lymphoblastic leukaemia.

3.1.2 Search strategy and eligibility criteria

I searched the databases Medline, Embase, Global Health and LILACS to identify studies reporting incidence of and survival after acute lymphoblastic leukaemia in children and adolescents. Databases were searched for publications from the last 5 years (from 2008 onwards) but also included relevant studies cited in these publications. I used the following approach: 1) Study population: “Child*” OR “paediatric” OR “pediatric” OR “boys” OR “girls” OR “infant*” OR “baby” OR “babies” OR adolescent*” AND 2) Acute lymphoblastic leukaemia terms: (“acute” OR “precursor”) AND (“lymphoblastic” OR “lymphoid” OR “lymphocytic”) AND “leukaemia” OR “leukemia” AND 3)

Disease outcome terms: “survival” OR “incidence”. I searched for articles published in English, Portuguese or Spanish due to my language proficiency. After duplicates had been removed, all titles and abstracts of publications identified in the course of my primary search were reviewed for relevance and eligibility criteria.

Eligibility criteria were: 1) original studies that report any length of survival from or incidence of acute lymphoblastic leukaemia in children and adolescents, 2) studies types were: cohort studies, clinical trials, reviews, systematic reviews and meta-analyses and cross-sectional studies. Conferences abstracts were excluded. Articles titles and abstracts were screened to select papers for full text screening.

3.1.3 Search results

My primary search identified 5,710 references. A total of 3,138 duplicates were removed using Endnote X6 and by hand searching, resulting in 2,572 references. From the remaining 2,572 references, 161 articles that appeared relevant from the abstract were reviewed in full and 26 were selected for inclusion in this literature review. The process of selection of the studies for this literature review is presented in Figure 3.1.

The 26 selected articles were published between 1998 and 2014, most in the last five years, and covered the period from 1962–2014. The study designs included population-based cohort, clinical trial, case-control and cross-sectional studies. Systematic reviews and one meta-analysis (on abandonment of treatment) were also included. The studies covered many

geographical areas, but most originated from Europe and the United States. The population age range varied from 0–19 years.

The main outcome of interest was survival to a specified time post-diagnosis. Data on disease biology, incidence, abandonment of treatment, relapse and treatment toxicity were also captured in some of the studies. Abandonment of treatment refers to children who either refused to begin potentially curative therapy at diagnosis or who interrupt therapy during active treatment. It does not include loss to follow-up after relapse or completion of therapy. The 26 studies identified from the literature search are summarised in Table 3.1.

In this Chapter, I report the main results from this literature review under a number of sub-headings as follows: biology and survival of ALL, incidence, improvement of survival over time, racial and ethnic differences in survival, survival among children with acute lymphoblastic leukaemia and Down syndrome, the survival gap between high income and low- and middle-income countries, abandonment of treatment, and the twinning programmes.

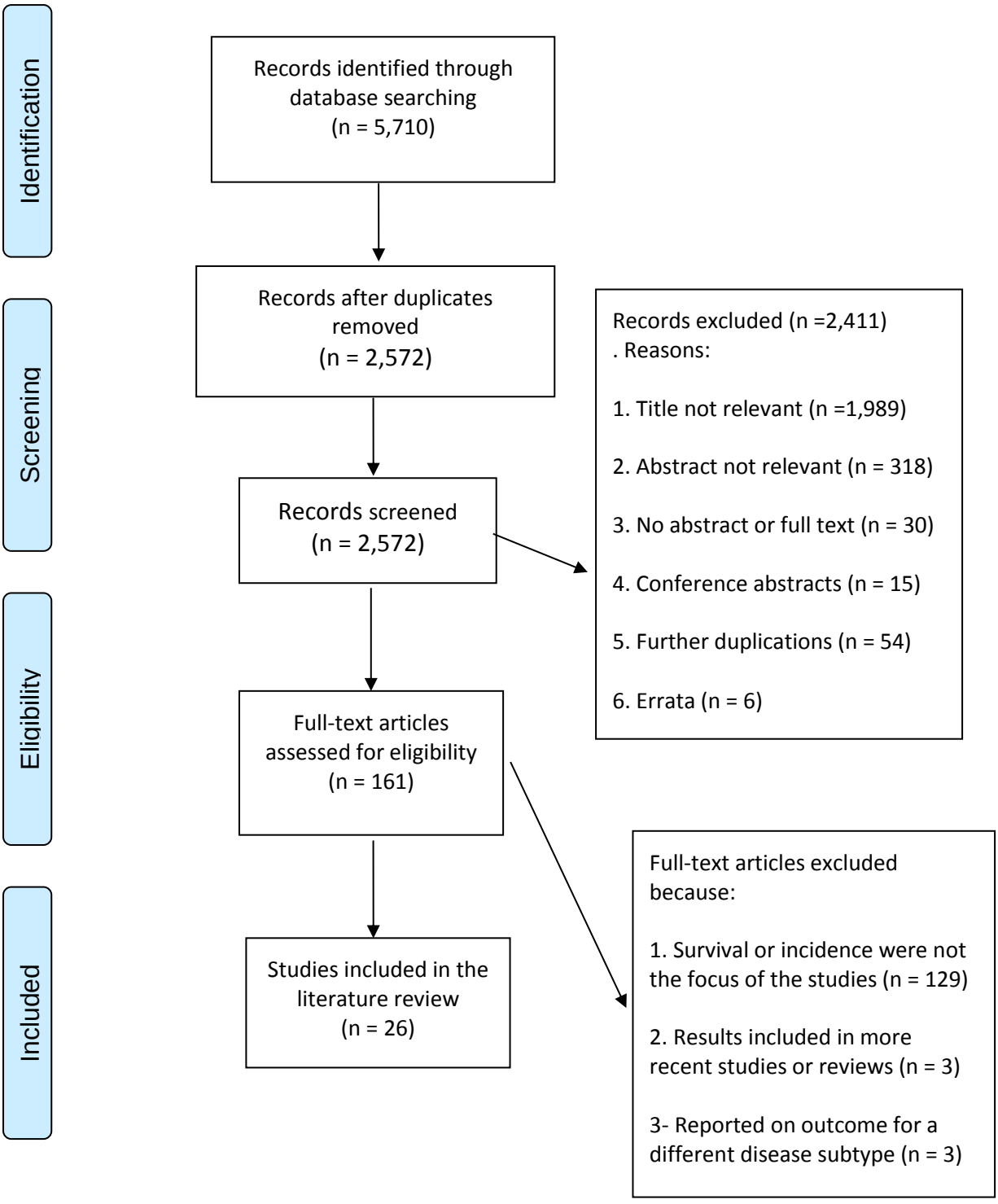

Figure 3.1: Process of selection of the studies for literature review on acute lymphoblastic leukaemia

Table 3.1: Characteristics of included studies and results of the literature review on acute lymphoblastic leukaemia

First author, year, setting	Study design	Period	Age (Y)	Number of cases (neoplasm)	Outcomes
01. Stiller CA, 1989, UK [109]	Population-based cohort	1971–1982	0–14	4,070 (ALL)	5–year-survival increased significantly from 37% during 1971–73 to 66% during 1980–82 and was significantly higher for children included in clinical trials than for those who were not.
02. Foucar K, 1991, US[110]	Hospital-based cohort	1969–1986	0–19	196 (ALL)	Median overall survival (ALL): 37 months in American Indian girls but 140 months in non-Hispanic white girls
03. Hesseling PB, 1995, South Africa[111]	Hospital-based cohort	1983–1993	0–14	112 (leukaemias)	5-year ALL survival: 63% for whites vs. 17% for blacks. Median survival time: 52 months for blacks vs. 9 months for whites
04. Dordelmann M, 1998, Europe (BFM)[112]	Clinical trials	1981–1995	0–14	61 (ALL DS) 4,049 (ALL NDS)	EFS: ALL DS = 58%, ALL NDS = 70%. When DS children received treatment similar to that for NDS children, survival improved (65% vs. 70%, respectively). For children under 6 years, EFS was similar among DS and NDS children (73 % vs. 74%) regardless protocol modification.
05. Chessells JM, 2001, UK[113]	Clinical trials	1971–1986	0–14	55(ALL DS) 3,596 (ALL NDS)	5-year survival: ALL DS = 73%, ALL NDS =82%. EFS: ALL DS = 53%, ALL NDS = 63%.
06. Kadan-Lottick NS, 2003, US[114]	Population-based cohort	1973–1999	0–19	4,952 (ALL)	5-year survival was worse among blacks, Hispanics and Native Americans than among whites: 84% for whites, 81% for Asians/Pacific Islanders, 75% for blacks, and 72% for American Indian/Alaskans and Hispanics.
07. Howard SC, 2004, Brazil[115]	Hospital-based cohort	1980–2002	0–17	375 (ALL)	5-year EFS increased progressively: 32% during 1980–89, 47% during 1990–94, and 63% during 1997–2002. Level of abandonment of treatment decreased from 16% to 0.5% over 22 years period.
08. Šteliarová-Foucher, 2004, Europe[24]	Population-based cohort	1970–1999	0–19	113,243 (multiple cancers); 35,570 (leukaemias)	Leukaemias: ASAIR =44.8 per million person-years, AAPC~1.4% per year over 30 years. 5-year survival for children increased from 44% in 1970s to 75% in 1990s), higher in the west than in the east.
09. Shah A & Coleman MP, 2007, England & Wales[25]	Population-based cohort	1911–2000	0–14	N/A (leukaemias)	Incidence rates increased from 38.3 in 1971–1975) to 46.1 in 1996–2000. MR decreased from 26.4 to 10.3 per 100,000. Average quinquennial change =1.5.
10. Arora RS, 2007, Asia, Africa, America Central/South[116]	Review	1980–2005	0–14	N/A (multiple cancers, including ALL)	For acute leukaemias: Level of abandonment of treatment varied from 16% in Brazil to 50% in India. Recently, level of abandonment of treatment reduced to <1% in Mexico under the public medical insurance and in Recife (Brazil) after the start of "twining programme".
11. Ribeiro RC, 2008, Africa, Asia, Europe and America South[117]	Cross-sectional	2005–2006	0–14	25,863 (9,747 ALL)	5-year survival: 5%-10% in Bangladesh, the Philippines, Senegal, Tanzania and Vietnam, 30% in Morocco, and 40%–60% in Egypt, Honduras, Ukraine, and Venezuela.
12. Coustan-Smith E, 2009, US & Italy[118]	Clinical trials	1992–2006	5–19	139 (T-ALL)	St. Jude: 10-year survival = 19% ETP ALL vs. 84% non-ETP ALL AEIOP: 2-year survival = 45% ETP ALL vs. 90% non-ETP ALL
13. Smith MA, 2010, US[6]	Population-based cohort	1975–2006	0–19	N/A (multiple cancers, including ALL)	ALL incidence rates increased from 1975 to 2006 (0.8% per year). 5-year relative survival rose from 61% (1975–1978) to 88.5% (1999–2002). Relative survival for infants remained poor compared to that for older children, but it increased significantly from 22% (1975–1978) to 62% (1999–2000).
14. Shah A, 2010, UK[119]	Population-based cohort	1971–2000	0–14	321 (DS) 12,310 (NDS)	5-years survival: ANLL DS: <1% (1970s) to ≥ 80% (1990s); ANLL NDS vs. DS= 84% vs. 64% (1996–2000). ALL DS: 7% (1970s) to 59% (1990s); ALL NDS= 83 % (1996–2000).
15. Perez-Saldivar ML, 2011, Mexico[38]	Hospital based cohort	2006–2007	0–14	228 (leukaemias)	ALL: ASAIR = 49.5 per million, highest for children aged 1–4 years (77.7 per million). AML ASAIR = 6.9 per million.

First author, year, setting	Study design	Period	Age (Y)	Number of cases (neoplasm)	Outcomes
16 Lightfoot TJ, 2012, UK[120]	Population-based cohort	1990–1997	0–14	1,559 (ALL)	HR of death =1.29 for children living in deprived areas (quintiles 4-5) compared to those living in affluent areas (quintiles 1-3). HR of death = 1.12 for children with father in the lowest vs. highest social class.
17. Kroll ME, 2012, UK[121]	Population-based cohort	1966–2005	0–15	54,650 (multiple cancers)	ASAIR increased by 0.7% per year, with step model increases in 1971, 1990 and 2002.
18. Pui CH, 2012, US[90]	Population-based & clinical trials	1992–2007	0–14	749 blacks, 5,381 whites (ALL)	SEER data: ALL 5-year survival: 73% for blacks vs. 86% for whites during 1992–2000; and 82% for blacks vs. 89% for whites during 2001–2007. St. Jude: survival did not differ significantly between black and white children
19. Pui CH, 2013, US[122]	Review (report on 15 clinical trials)	1962–2007	0–18	2,852 (ALL)	10-year survival improved from 11% (1962–1966) to 91% (2000–07) in the US during the last 5 decades. 5-year survival = 93.5% during 2000–2007.
20. Kersten E, 2013, Tanzania[123]	Hospital-based cohort	2008–2010	0–18	106 (81 ALL and 25 AML)	2-year EFS: ALL = 33%, AML = 0%. 10 children died before start of treatment; 19 died of toxicity. Abandonment of treatment=8%.
21. Gatta G, 2013, Europe[5]	Population-based cohort	1999–2007	0–14	59,579 (19,097 ALL)	5-year survival (all cancers) in eastern Europe rose from 65.2% (1999–2001) to 70.2% (2005–07). For ALL, 5-year survival increased from 82.2% (1999–2001) to 87.6% (2005-2007) with disparities among regions.
22. Gupta S, 2013, Asia, America Central/South[124]	Systematic review & meta–analysis	2010–2011	0–18	10,494 (leukaemias)	Level of abandonment of treatment ranged from 0–74%. For ALL, level of abandonment of treatment was 29% I n lower-MICs and 2% in upper-MICs, but highly heterogeneous in lower-MICs.
23. Rivera-Luna R, 2013, Mexico[125]	Hospital-based cohort	2007–2010	0–18	8,963 (3,748 ALL)	Abandonment of treatment = 27% (2000) vs. 4.1% (2011), stable since 2007. For leukaemias alone, IR= 75.3 per million per year (year 2010). MR declined from 5.93 to 5.4 per 100,000 during the study period.
24. Perez-Cuevas R, 2013, Mexico[126]	Hospital based cohort	2006–2009	0–14	3,821 (1,774 ALL)	3-year survival: 50.0% for ALL and 30.5% for AML. Wide ALL survival variation within the five Mexican regions: from 21.3% in the south-southwest to 64.6% in northwest.
25. Valery P, 2014, North America, Oceania and Africa[127]	Review (population- and hospital-based)	1980–2013	0–14	N/A (multiple cancers, including ALL)	ALL 5-year survival: significantly lower in IP than non-IP in the US, as well as in New Zealand and Pacific Island Polynesians. South Africa: survival much lower in blacks compared to whites.
26. Buitenkamp T, 2014, Europe[128]	Report on 16 clinical trials (BMF and Dutch group)	1995–2004	0–18	653 (DS ALL) 4445 (NDS ALL)	8-year EFS and OS = 64% and 74% (DS) and 81% and 89% (NDS). Relapse was the main prognostic factor for lower survival.in DS-ALL. 2-year TRM was 7% DS vs. 1% NDS [patients

Abbreviations: AAPC, annual average percentage change; AEIOP, Italian Paediatric Haematology-Oncology Association; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ANLL, acute non-lymphoblastic leukaemia; ASAIR, age-standardised annual incidence rates; BFM, Berlin-Frankfurt-Münster Study Group; DS, Down syndrome; EFS, event-free survival; ETP, early T-cell precursor; HR=hazard ratio of death; IP, indigenous populations; MICs, middle income countries; MR, mortality rates; NDS, non-Down syndrome; SEER, Surveillance, Epidemiology and End Results; St. Jude, St. Jude Children's Research Hospital; US, United States; UK, United Kingdom.

3.1.4 Main findings

The biology and survival of acute lymphoblastic leukaemia

Genetic studies have been essential to better understand the characteristics, behaviours and prognosis of malignancies. Childhood acute leukaemias have been thoroughly studied and are, to date, the most understood neoplasm from a genetic perspective.[7] This has allowed the development of new therapies that have substantially improved survival after acute myeloid leukaemia and, even more so after acute lymphoblastic leukaemia. Milestones in biologic research of acute lymphoblastic leukaemia mostly predate 2000. They are summarised in Table 3.2.

Table 3.2: Landmarks in understanding the biology of acute lymphoblastic leukaemia. Source: Pui et al., *Semin Hematol* 2013[7]

Year	Biologic advance
1958	First cytogenetic study in ALL[129]
1970	First report of Philadelphia chromosome-positive ALL[130]
1973	First identification of T-cell by spontaneous rosette formation with sheep erythrocytes[131]
1978	Classification of ALL by chromosome number > 50 (hyperdiploidy) is associated with prolonged remission duration[132]
1981	Immunologic monitoring of residual leukaemia[133]
1984	First identification of immunophenotype-specific chromosome translocations: t(11;14) in T-cell ALL and t(1;19) in pre-B ALL[134]
2002	First genomic-wide profiling of gene expression[135]
2007	First genomic-wide study of changes in DNA copy number[106]
2009	Germline genetic variants associated with the development of ALL[136, 137]
2012	First whole-genome sequencing study to identify driver mutations in early T-cell precursor ALL[138]

According to the WHO classification[29] reviewed in section 2.3.2, acute lymphoblastic leukaemia is divided into two major immunophenotypic subtypes: precursor B-cell (B-ALL) and precursor T-cell (T-ALL). B-ALL is the most common subtype, accounting for about 85% of all cases of acute lymphoblastic

leukaemia. Nearly all B-ALL cases can now be classified genetically, which facilitates risk-directed therapy.[7] By contrast, the T-ALL subtype corresponds to 15% of all cases acute lymphoblastic leukaemia, often presents with poor prognostic factors (e.g. older age) and is usually treated with a standard protocol rather than targeted therapies. With intensive chemotherapy, the prognosis of children with T-ALL has increased considerably and is currently fairly similar to that of B-ALL. However, among T-ALL cases, there is a very high-risk subgroup called early T-cell precursor ALL (ETP ALL).

Coustan-Smith et al.[118] analysed data from 239 children with T-ALL enrolled in clinical trials at St. Jude Children's Research Hospital in the United States and in the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) ALL 2000 trial. At St. Jude, 12% of these children had ETP-ALL, and overall 10-year survival was much lower than that of children with non-ETP ALL (19% vs. 84%, respectively). In children enrolled in the AIEOP ALL-2000 trial, the prognosis of children with ETP ALL was also dismal (2-year overall survival was 45% vs. 90% for those with non-ETP ALL).

In populations with higher incidence of childhood acute lymphoblastic leukaemia (e.g. whites in developed countries) common ALL (early precursor B-cell) accounts for about 70% of acute lymphoblastic leukaemia cases. In low incidence populations such as India and Nigeria, early precursor B-cell ALL corresponds to only 30% of the cases, and T-ALL has a higher relative incidence. The higher incidence of common ALL among affluent populations suggests that environmental factors associated with high socioeconomic status may play an important role in the aetiology of acute lymphoblastic leukaemia.[139]

Incidence of acute lymphoblastic leukaemia: increasing trends

Several studies reported that the incidence of childhood acute lymphoblastic leukaemia has been increasing since the 1970s, at least in Europe (except Nordic countries) and in the United States. In Europe, age-standardised incidence rates (ASIR) increased on average, by 1.4% per year over 30 years.[25, 44] In the United States, ASIR increased by 0.5%–0.8% over 25–31 years.[6, 23] This increase was observed in both sexes, in all age groups examined (<1y, 1–4 y, 5–9y and 10–14y) and, in the United States where data were available, in both blacks and whites.

Some controversy exists regarding whether this reported increase of acute lymphoblastic leukaemia incidence is artefactual (e.g., due to better diagnosis) or real. Kroll et al.[121] examined the trends of childhood cancer incidence, including leukaemias, observed in Great Britain from 1966 to 2005, and compared it with changes in registration procedures. For leukaemias, incidence rates increased by 0.7% per year during this period. The step model showing increased incidence in 1971, 1990, and 2002 coincided with improvement in general cancer registration. For instance, a reviewed recording process was introduced on 1 January 1971, the responsibility for cancer registration was transferred from area of treatment to area of residence on 1 July 1978, and in 2001, the Department of Health developed a plan to improve the effectiveness of cancer registries. In another study, Kroll et al.[140] reported that among children from poor communities in Great Britain, there was clinical evidence for an under-diagnosis of acute lymphoblastic leukaemia during the 1980s and 1990s among children who died due to severe infections. These suggested that, at least in part, the increased incidence was secondary to improved registration.

Adamson et al.[141] also suggested that the increase in acute lymphoblastic leukaemia incidence in Europe was largely due to improvement in cancer registration, and this was a result of the enrolment of most children with cancer in clinical trials. The fact that increased rates occurred in almost all malignancies is consistent with better cancer registration. Despite these reports, there is strong evidence to support the increased incidence rates of acute lymphoblastic leukaemia being real.

Firstly, studies that showed an increasing incidence of childhood leukaemia used large populations and relied on standardised high-quality data collected over 25–40 years. Therefore, the possibility of bias is unlikely. For example, Šteliarová-Foucher et al.[16] compared data from 63 European population-based registries containing records of 131,243 children and adolescents (0–19 years), including 35,570 leukaemias. Age-standardised incidence rates were calculated and compared. Lymphoid leukaemias rates increased by ~1.4% per year over 30 years in this cohort.

Secondly, improvements in diagnostic methods observed in the last 3 decades are likely to explain only a small part of the reported increase in acute lymphoblastic leukaemia incidence. In the Kroll et al.[121] study cited above, for acute lymphoblastic leukaemia the improvement in diagnostic approach that occurred in 1985 was restricted to immunohistochemistry. This is used to identify subtypes of leukaemias, but not to make the initial leukaemia diagnosis. The same is valid for other diagnostic techniques developed later that helped to stratify risk and guide therapy.

Thirdly, according to one study based on a high-quality population-based registry in Britain, during 1980–1996, the average annual percentage change in

incidence rates of acute lymphoblastic leukaemia was 1.4%. It was suggested that this was due to an increase of the precursor B-cell sub-type. This increase was not followed by an increase of other subtypes of acute lymphoblastic leukaemia or acute myeloid leukaemia, making it unlikely that the acute lymphoblastic leukaemia increased incidence is simply secondary to an improvement in completeness of registration.[142]

Finally, another study analysed data on childhood leukaemia over most of the twentieth century, and examined incidence and mortality trends by age, sex and 5-year calendar periods, in England and Wales.[25] Incidence increased 4% every 5 years from the early 1971 to 2000, mainly in infants (<1 year old) and children aged 1–4 years. The assumption that a lethal infection could have "masked" a diagnosis of leukaemia in the beginning of the century leading to leukaemia under-diagnosis,[143] does not explain the increase in leukaemia incidence during 1971–2000. The authors showed that considering the decrease in infant mortality in this period, children that survived up to 5 years would need to have had a 20-fold higher incidence of leukaemia than the rest of the population, to account for the incidence growth. The mortality rates declined considerably during this period, reflecting the extraordinary improvement in survival during the last 50 years. However, the incidence rates continued to increase, supporting the hypothesis that the rise in acute lymphoblastic leukaemia incidence was real (Figure 3.2).

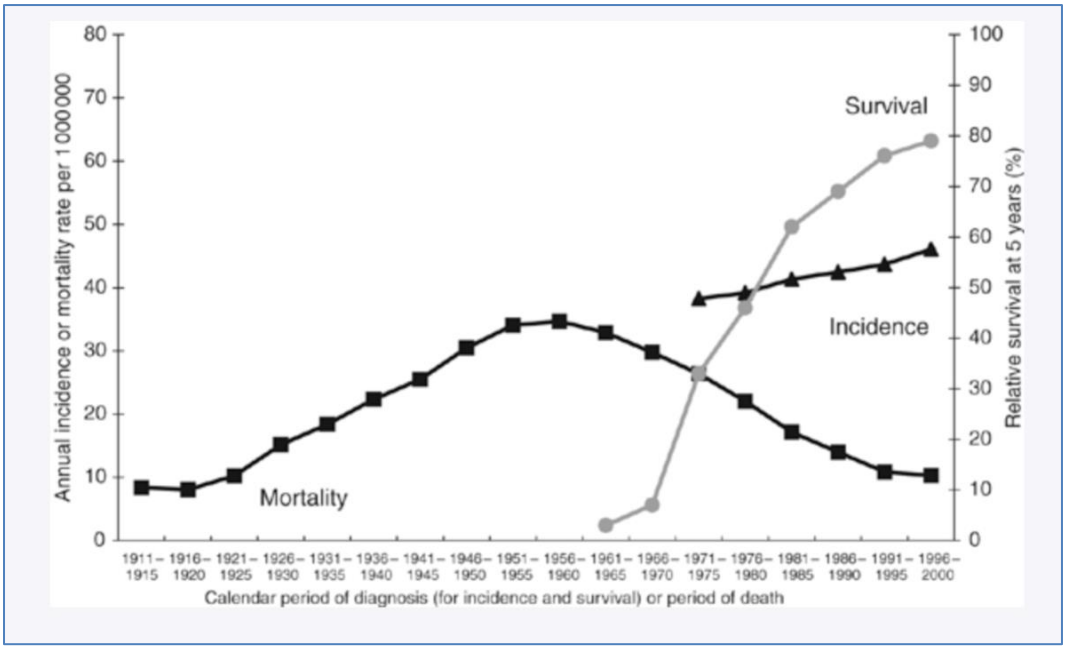

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Figure 3.2: Trends in leukaemia incidence, survival and mortality in children, England and Wales, 1971–2000. Source: Shah and Coleman, *Br J Cancer* 2007[25]

Remarkable improvement in survival from acute lymphoblastic leukaemia in the last 50 years

Acute lymphoblastic leukaemia was consistently fatal during the 1960s. Today, 5-year survival in the developed countries is, at the population-based level,[5, 7, 19] approximately 80%–90% and up to 93.5% in clinical trials.[7]

This outstanding achievement was driven by a multidisciplinary treatment approach, novel chemotherapeutic agents, a better understanding of the biology of acute lymphoblastic leukaemia, the development of new diagnostic methods and more precise risk stratification. Because acute lymphoblastic leukaemia is a complex disease, responses to treatment may vary considerably even among children with the same disease phenotype. Precise risk stratification is key for the provision of individualised treatment to children with acute lymphoblastic leukaemia: more intensive and prolonged regimens should be given to high-risk

patients (10%–30% of patients), whilst a less intensive protocol should be applied for favourable-risk patients, preventing under- or over-treatment, respectively.

In high-income countries, collaborative clinical trials and standardised protocols have led to a rapid increase in survival. Stiller and Draper[109] compared the survival trends of 4,070 children with acute lymphoblastic leukaemia treated in the United Kingdom Medical Research Council trials (UKALL) during 1971–1982. Five-year survival increased substantially from 37% during 1971–1973 to 66% during 1980–1982. The impact of the inclusion of children with acute lymphoblastic leukaemia in clinical trials was evident: survival was significantly higher for these children than for those not included in the UKALL trials. Moreover, for these children, there was no survival difference based on treatment at centres of different sizes. However, for children not included in clinical trials, survival was higher among those treated at larger centres with high volumes of patients (average of six new children per year) than for those treated at smaller centres (less than a patient per year).

The most significant therapeutic advances resulting from clinical trials are summarised in Table 3.3. Importantly, these improvements associated with the use of risk-directed therapy led to a reduction or elimination of some adverse prognostic factors, such as high initial white blood cell count, Philadelphia chromosome-positive ALL, a subgroup of children with Down syndrome, black race, and male gender. For example, blacks and male children now have similar survival as white and female children, at least in some centres in developed countries (section 2.5.1).[90, 144]

Table 3.3: Landmark advances in the development of therapy for childhood acute lymphoblastic leukaemia. Source: Pui et al., *Semin Hematol* 2013[7]

Year	Therapeutic advance
1948	"Transient remissions" induced by aminopterin[145]
1971	Combination chemotherapy and effective central nervous system (CNS)-directed therapy cure approximately 50% of patients[146]
1981	Re-induction treatment improves outcome[147]
1982	Triple intrathecal therapy with methotrexate, hydrocortisone, and cytarabine may effectively substitute prophylactic cranial irradiation in some patients[148]
1983	Post-remission weekly high-dose asparaginase improves outcome[149]
1983	Intermediate-dose methotrexate with leucovorin rescue decreases systemic and testicular relapses[150]
1991	Dexamethasone is more effective than prednisone in preventing CNS relapse[151]
1995	Inherent genetic polymorphisms in gene encoding thiopurine methyltransferase influence mercaptopurine toxicity[152]
1998	Individualised methotrexate dose improves outcome[153]
2009	Effective systemic and intrathecal chemotherapy can eliminate the need for prophylactic cranial irradiation in all patients[144]
2009	Imatinib improves early treatment outcome in Philadelphia chromosome-positive ALL[154]

Racial and ethnic differences in survival from acute lymphoblastic leukaemia

Cancer survival inequalities between blacks and whites in the United States have been well documented for different types of cancer in adults and children.[155, 156] Survival disparities between black and white children with acute leukaemia have been also reported in Africa.[111, 157] For example, in a paediatric oncology unit at Tygerberg Children's Hospital in South Africa, 77 children (0–14 years) diagnosed with acute lymphoblastic leukaemia during 1983–1993, were treated with the Berlin-Frankfurt-Münster Study Group (BFM) ALL 1983 protocol. Among these children, 38% were white, 46% so-called coloured, and 16% were blacks. Five-year survival was 63% among whites, 38% among coloured and a dismal 17% among blacks (*P* value < 0.01). The median survival time (the length of time from the date of diagnosis of leukaemia in which half of patients are alive) was 52.5 months for whites but only 9 months for blacks. The number of children with

acute lymphoblastic leukaemia was small, but the data from this hospital-based registry were considered reliable by the authors (less than 3% of loss to follow-up and accurate information on disease presentation and outcome). The differences in survival between the three groups could not be explained by differences in prognostic factors or treatment compliance.[111]

Several factors have been suggested to explain the racial survival gap, such as socioeconomic status, biologic or cultural factors, treatment responses and patients' unique genetic characteristics. Recently, Pui et al.[90] have demonstrated that when black children receive intensive risk-based therapy and comprehensive supportive care, they can achieve similar survival as white children, thereby reducing the impact of some adverse factors, such as high leukocyte count, T-cell immunophenotype, chromosome translocation t(1,19), and ancestry-related relapse hazard. They compared survival from childhood cancer between children treated at St. Jude Children's Research Hospital and children registered in one of the cancer registries of the National Cancer Institute's SEER programme during two periods (1992–2000 and 2001–2007). For acute lymphoblastic leukaemia, 5,222 children (0–14 years) were analysed using data from the SEER programme, and 908 children from St. Jude. Survival was lower, in both periods, for black children registered in the SEER programme. At St. Jude, however, survival did not differ significantly between races in either period (Table 3.4). Type of health insurance coverage was used as a proxy for financial status of those children at St. Jude. Black children were more likely to have public insurance than private insurance, suggesting lower socioeconomic status. In the SEER programme, there was no information on socioeconomic status, disease clinical feature, the proportion of children treated in specialised

centres or on the proportion treated by protocol-directed therapy, precluding some specific comparisons with data from St. Jude. This is a tertiary referral hospital and is expected to treat a greater proportion of high-risk children. Despite the less favourable prognostic factors, black children had similar survival as white children. This study suggests that equivalent treatment can reduce or eliminate racial disparities among children with acute lymphoblastic leukaemia as discussed earlier in section 2.5.

Table 3.4: Comparison of 5-year survival between black and white children with acute lymphoblastic leukaemia. Data from St. Jude and SEER programme, 1992–2007. Adapted from Pui CH et al., *J Clin Oncol* 2012[90]

	1992–2000					2001–2007				
	Blacks		Whites			Blacks		Whites		
Dataset	***N***	**5-y OS**	***N***	**5-y OS**	***P*-value**	***N***	**5-y OS**	***N***	**5-y OS**	***P*-value**
SEER	233	72.8%	1,931	85.9%	< 0.01	358	82.1%	2,700	89%	< 0.01
St. Jude	82	81.6%	370	85.7%	0.58	76	89.4%	380	93.2%	0.41

Abbreviations: OS, overall survival; SEER, Surveillance, Epidemiology and End Results; St. Jude, St. Jude Children's, Research Hospital. The *P*-values for testing differences in survival between black and white patients.

A recent systematic review by Valery et al.[127] assessed the international burden of childhood cancer in indigenous populations. Although information about ethnicity is scarce in most countries and the available data may lack accuracy and quality, significant differences were reported. Most of the studies showed that survival from leukaemias was usually lower for indigenous children than for non-indigenous children. For example, a hospital-based study evaluated 196 children aged 0–19 years when diagnosed with acute lymphoblastic leukaemia, at the University of New Mexico affiliated institutions in the United States. Survival was compared among three ethnic groups (Hispanic and non-Hispanic whites, and American Indians) during 1969–1986. Median overall

survival for children with acute lymphoblastic leukaemia was considerably lower in indigenous populations than non-indigenous populations: only 8 months for American Indian boys and 37 months for American Indian girls, but 36 months for non-Hispanic white boys and 140 months for non-Hispanic white girls.[110]

In a population-based study[114] of 4,952 children and adolescents (0–19 years) diagnosed with acute lymphoblastic leukaemia and registered in the SEER programme between 1973 and 1999, survival was compared among five ethnic groups: white, black, Hispanic, Asian/Pacific Islander, and American Indian/Alaskan Native. After adjusting for age, sex and treatment era, 5-year survival was lower among blacks, Hispanics and Native Americans than among whites and Asians: 84% for whites, 81% for Asians/Pacific Islanders, 75% for blacks, and 72% for American Indian/Alaskans and Hispanics.

The authors of the systematic review above[127] suggested that the most likely causes of worse prognosis among indigenous children were: lack of cancer awareness among this population, lack of availability of treatment different from traditional indigenous medicine, cultural factors, treatment refusal, and abandonment of treatment. In paediatric oncology, treatment adherence has been reported to vary from 41% to 98%[158-160] and abandonment of treatment is considered the major cause of treatment failure in low-income countries.

Moore et al.[161] conducted a systematic review of cancer aetiology and patterns among indigenous population in South American countries. They obtained information on indigenous adults, but there was no information on indigenous children. The authors pointed out the need for improvement of cancer registration in low- and middle- income countries in general, as well as among indigenous populations in these countries. In fact, data collected by the

International Agency for Research on Cancer (IARC) contain information on indigenous population from only two countries: the United States and New Zealand.

Survival from acute lymphoblastic leukaemia among children with Down syndrome

Most researchers have found that children with Down syndrome have a 10–20 fold increased risk of developing acute lymphoblastic and myeloid leukaemias over children without Down syndrome.[60] In general, acute lymphoblastic leukaemia in children with Down syndrome has inferior outcome than in other children.[162] This has mostly been attributed to treatment toxicity, particularly infectious complications, including bacterial, viral and fungal infections. Consequently, these children tend to receive less intensive chemotherapy prompting them to a higher risk of relapse.[52]

A population-based study by Shah et al.,[162] evaluated trends in 5-year survival in children (0–14 years) with and without Down syndrome, diagnosed with leukaemia from 1971 to 2000 in Great Britain. This study showed that for acute non-lymphoblastic leukaemia (ANLL), including acute myeloid leukaemia, 5-year survival increased significantly from less than 1% in the early 1970s to 80% or over in the 1990s. This improvement was even higher for Down syndrome children than for non-Down syndrome children (84% vs. 64%) during 1996–2000. However, for acute lymphoblastic leukaemia, survival for children with Down syndrome increased from 7% to 72% during 1991–1995, but decreased later, and remained lower than that for non-Down syndrome children (59% vs. 83%) during 1996–2000.

The authors suggested that the poor prognosis observed in children with Down syndrome and leukaemias in the 1970s and early 1980s were associated with lack of appropriate treatment and less recruitment to clinical trials. About 38% of children with Down syndrome and acute leukaemias received minimal treatment or were advised not to receive any treatment, and died. During 1971–2000, recruitment of children with Down syndrome and leukaemias into clinical trials was lower than that of children without Down syndrome: for acute lymphoblastic leukaemia, the difference was 40% vs. 70%, and for acute myeloid leukaemia it was 23% vs. 50%, respectively.

During the mid-1980s, it became more common to treat Down syndrome children on standard leukaemia protocol. Several clinical trials[112] have shown that when intensive treatment, comprehensive supportive care and rigorous control of infections are provided, outcomes in children with Down syndrome tend to be similar to that of children without Down syndrome.

In Europe, four consecutive clinical trials conducted by the BFM group,[112] from 1981 to 1995, compared treatment outcome of 61 children aged less than 15 years with acute lymphoblastic leukaemia and Down syndrome, to 4,049 children with acute lymphoblastic leukaemia without Down syndrome. Six-year event-free survival was lower among children with Down syndrome than those without Down syndrome (58% vs. 70%, *P* value = 0.14). However, event-free survival was similar when intensive chemotherapy was administered and optimal supportive care was provided (65% vs. 70%, *P* value = 0.66). For children under 6 years, event-free survival was similar between the two groups regardless of protocol differences (73 % vs. 74%, *P* value = 0.7). These findings suggest that, given intensive treatment, children with acute lymphoblastic leukaemia and Down

syndrome can achieve the same survival than that of children with acute lymphoblastic leukaemia without Down syndrome, but these results did not reach statistical significance.

Two clinical trials conducted by the UK Medical Research Council[113] from 1985 to 1997 showed worse event-free survival and overall survival in 55 children aged 15 years or less with acute lymphoblastic leukaemia and Down syndrome, compared to 3,596 children with acute lymphoblastic leukaemia without Down syndrome: 5-year survival was 73% vs. 82%, and 5-year event-free survival was 53% vs. 63% respectively.

Recently, Buitenkamp et al.[128] conducted a retrospective analysis including a large sample of 653 children (0–18 years) with Down syndrome and acute lymphoblastic leukaemia enrolled in 16 international trials, from 1995 to 2004. They identified a sub-group of children with Down syndrome with more favourable prognosis: children aged under 6 years, with white blood cell count $<10X10^9/L$, and with the cytogenetic abnormalities ETV6-RUNX1 and hyperdiploidy. Children with these cytogenetic aberrations comprised 12% of children with Down syndrome and acute lymphoblastic leukaemia, and are probably eligible for future treatment reduction in order to avoid toxicity, the major cause of mortality in this study cohort. Except for this specific sub-group, less intensive treatment has not been recommended for the remaining children with Down syndrome and acute lymphoblastic leukaemia due to the high potential risk of relapse.

The survival gap between high income and low- and middle-income countries

About 80% of children with cancer live in low- and middle-income countries and approximately 94% of all childhood cancer deaths occur in these countries.[163] Despite the extraordinary increase in survival from acute lymphoblastic leukaemia in the last half century, many children still die from this treatable disease, mainly in resource-poor areas. Survival from childhood acute lymphoblastic leukaemia varies widely worldwide as demonstrated below.

High-income countries

Important survival variations exist even among high-income countries. Gatta et al.[5] estimated 5-year survival from childhood cancers in 59,579 European children (19,097 acute lymphoblastic leukaemia cases), aged 0–14 years, during 2000–2007. This population-based study collected data from 74 registries in 29 European countries. Survival improved in all regions studied, but the greatest improvement was in Eastern Europe: 5-year survival for multiple cancers increased from 65.2% (1999–2001) to 70.2% (2005–2007). However, wide disparities within European areas persisted despite major improvements in diagnosis and treatment seen in the last few decades. Five-year survival for acute lymphoblastic leukaemia was 80.3% in Eastern Europe but it ranged from 86.7% to 90.1% in other European regions during 2005–2007. The authors suggested that the poorer survival in Eastern Europe might be due to the lack of government funding for cancer control, absence of national cancer plans, and inadequate access to optimal treatment.

Another European study conducted by Lightfoot et al,[120] investigated the association between SES and survival among children (0–14 years) diagnosed with ALL during 1990–1997. An area-based deprivation index and father's occupation information were used as surrogates of SES. Overall survival was significantly lower for children living in deprived areas (quintiles 4 and 5) than in affluent areas (quintiles 1–3) (HR = 1.29, 1.05–1.57). Similarly, survival was somewhat inferior for children with a father from the lowest social class than the highest social class (HR = 1.12, 0.97–1.29) (Figure 3.3). The authors highlighted that these findings are of particular importance considering that in the UK all children have access to the same treatment guaranteed by the National Health Service (NHS), thus modifiable factors such as adherence to treatment may play a role in the survival differences observed.

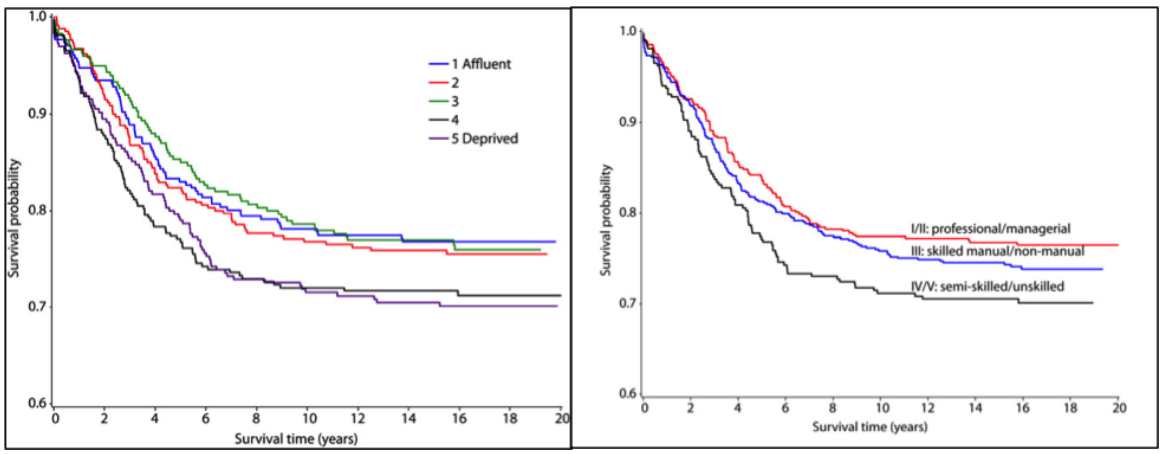

Figure 3.3 :Overall survival of children (0–14 years) with ALL in the UK, by area-based deprivation quintiles at diagnosis (left) and father's employment status, (right), 1990–1997. Source: Lightfoot et al., *Eur J Cancer* 2012[120]

In the United States, Smith et al.[6] analysed data from the SEER programme and estimated 5-year relative survival after acute lymphoblastic leukaemia and other cancers, in children and adolescents (0–19 years), during 1975–2006. Relative survival increased from 61% (1975–1978) to 89% (1999–

2002). For infants (<1 year) with ALL, relative survival increased substantially from 22% (1975–1978) to 62% (1999–2002), but remained lower than that of older children.

In a recent review, Pui et al.[7] reported the results of 15 clinical trials conducted at St. Jude Children's Research Hospital, which included 2,852 children (1–18 years) with acute lymphoblastic leukaemia, during 1962–2007. Ten-year survival improved from 11.1% (1962–1966) to 91.1% (2000–2007) in the United States over these four decades. During 2000–2007, 5-year survival was as high as 93.5%. The author discusses that protocol-directed therapy with children enrolled in clinical trials is essential for optimal outcomes. Moreover, genome-wide studies as well as minimal residual disease measurements are important for risk stratification and target therapy. To date, cranial irradiation has been reserved for those children who have high-risk of central nervous system relapse, and has been even abandoned at St. Jude.[144]

Although in the United States survival in children with acute lymphoblastic leukaemia is one of the highest in the world, several studies have documented survival disparities among children with cancer and different races and ethnicities (described above). Similarly to Europe, most children with cancer in the United States are enrolled in clinical trials as soon as they are diagnosed with leukaemia, and are referred for treatment at specialised paediatric centres. This has long been considered the "gold-standard" practice for children with cancer, including acute lymphoblastic leukaemia.

Low- and middle-income countries

Survival varies widely between and within low- and middle-income countries. A few examples are described as follows. In Tanzania, as in most countries in Africa, there is no cancer registry, and hospital records are of poor quality. In 2004, in order to provide free cancer care to all children in the country, the Tanzanian government opened a paediatric ward with 17 beds at the Ocean Road National Cancer Institute in Dar es Salaam. A recent retrospective study[123] examined data on 106 children aged 0–18 years diagnosed with acute leukaemia (81 acute lymphoblastic leukaemia and 25 acute myeloid leukaemia) during 2008–2010. Two-year event-free survival for acute lymphoblastic leukaemia was still low (33%), but much better than in 2005, when only 1 out of 20 children survived one year. For acute myeloid leukaemia, 2-year event-free survival was a 0%. In this study, ten children died before the start of treatment, 19 died of treatment toxicity and 8 children abandoned treatment.

The authors suggested that the main reasons for the poor outcomes were related to delays in seeking and receiving treatment, limited access to chemotherapy drugs and diagnostic supplies, insufficient beds for paediatric oncology, abandonment of treatment, and lack of health personnel. In Tanzania, there was only one paediatric oncologist for the entire country, located at Dar es Salaam. In addition, one third of children with leukaemias were malnourished, and one third had concomitant malaria, both factors that might have contributed to the poor leukaemia prognosis.

Asia, Africa, Latin America and Europe (Ukraine)

Ribeiro et al.[164] performed a cross-sectional study aimed to assess the paediatric oncology services in ten low- and middle-income countries, and estimate survival from childhood cancers. Population-based and hospital based-registries were scarce in these countries. A field survey of clinicians, health officials and health care managers was conducted during 2005–2006. The more relevant findings in this study were: (1) 5-year "postulated" survival for children under 15 years with all cancers combined, was much lower than survival in high-income countries: 5%–10% in Bangladesh, the Philippines, Senegal, Tanzania and Vietnam; 30% in Morocco; and 40% in Egypt, Honduras, Ukraine and Venezuela; (2) the number of children cared for by individual paediatric oncologists varied from 1:10 to 1:75; (3) annual government expenditure on health was the best predictor of survival; (4) diagnostic testing and treatment supplies were often lacking or in short supply.

Mexico

Mexico has one of the highest incidence rates of childhood leukaemia globally. The Mexico National Registry for Childhood Cancer started in 2006. During the period 2006–2007, the average annual incidence rate of acute lymphoblastic leukaemia was 49.5 per million in Mexico City, among the highest in the world.[38] An effective treatment of acute leukaemia takes, on average, 2 to 3 years, and it is complex and expensive. This prevents many children from developing countries from receiving appropriate treatment. In 2006, a public medical insurance programme was created in Mexico, aimed at providing optimal

standardised treatment for children with cancer: the Fund for Protection against Catastrophic Expenditures (FPGC).

Rivera-Luna et al.[125] evaluated the impact of the FPGC on children with cancer aged 18 years or less, enrolled in one of the 47 accredited Mexican institutions during 2007–2010. They reported that 8,963 children enrolled in this public medical insurance programme were diagnosed with cancer (3,748 with acute lymphoblastic leukaemia). Across Mexico, the incidence rate of acute leukaemia alone was 75.3 per million per year (year 2010). Several improvement in outcomes were observed after the implementation of the programme: (1) although still elevated, standardised mortality rates declined from 5.93 to 5.4 (per 100,000) during the study period; (2) level of abandonment of treatment decreased from about 27% (2000) to 4.1% (2011), and it has remained stable since 2007; (3) adherence to treatment (including following the prescription, using drugs regularly and as recommended, as well as accuracy of administration[159]) increased from 48% before the FPGC to 95% in 2011. In conclusion, the FPGC had a positive impact during the first years of implementation, allowing uninsured children to receive cancer treatment. The authors emphasised that further improvements are needed in order to decrease the burden of paediatric cancer in this population.

In another study, Perez-Cuevas et al.[126] estimated 3-year survival of 3,821 children (0–14 years) with cancer treated under the FPGC during 2006–2009. The proportion of children covered increased from 3.3% in 2006 to 55.3% in 2009, without evidence of further increase of children assisted. Acute lymphoblastic leukaemia accounted for 46.4% of the cases and acute myeloid leukaemia for 7.4%. Three-year survival was far lower than that of developed

nations: 50.0% for acute lymphoblastic leukaemia and 30.5% for acute myeloid leukaemia. Moreover, childhood leukaemia survival varied dramatically among geographic areas of Mexico: from 64.6% in northwest to 21.3% in the south-southwest.

Ribeiro, RC[165] argues that the south-southeast region of Mexico has the highest estimated incidence of children with cancer, but less than 40% of these children were registered in the FPGC. He highlighted that this region has the lowest Human Development Index (HDI, an index that combines three indicators of human development: life expectancy, educational attainment and income) compared to other geographic areas of Mexico, suggesting that the FPGC has not been as effective and equally distributed in the more deprived areas of Mexico as it has been in the more affluent areas of the country.

Finally, the recent published CONCORD-2 study,[19] a global surveillance of cancer survival, reported 5-year net survival after acute lymphoblastic leukaemia on 74,343 children aged 0–14 years from about 215 registries in 53 countries. Five-year net survival was as high as 90% in Canada, Austria, Germany, Norway and Belgium, and about 80%–89% in the United Sates and various other developed countries on different continents. Strikingly, survival was less than 60% in most low-and middle-income countries, including Indonesia, Lesotho, and Mongolia.

The problem of abandonment of treatment in low- and middle-income countries

Abandonment of treatment is an established cause of treatment failure among children with cancer in low- and middle-income countries.[166] Arora et al.[116]

reviewed the literature to evaluate the level of abandonment of treatment, possible causes and potential opportunities for improvement in these disadvantaged populations. Their findings showed that abandonment of treatment is widespread in the developing world, involves all childhood cancers and is more evident in Asia (e.g. India and Turkey), Africa (e.g. Morocco), and many countries in Central and South America. For acute leukaemias, level of abandonment of treatment varied from 16% in Brazil to 50% in India. More recently, level of abandonment of treatment was reported as less than 1% in Mexico under the FPGC, and also in Recife, Brazil due to the impact of twinning programmes (described below).

In high-income countries, abandonment of treatment is rare. When this happens, the authors suggested that it might result from the child's physical discomfort, parents' poor understanding about the disease and its treatment, and parents' fear and uncertainty regarding treatment benefits.

By contrast, in low- and middle-income countries, a greater number of reasons were suggested to explain abandonment of treatment, including (1) lack of financial resources, hospital facilities and trained health professionals; (2) lack of parental education and cancer awareness; (3) long distances from home to treatment centre; and (4) religious beliefs.

Gupta et al.[124] performed a systematic review and meta-analysis to examine the problem of abandonment of treatment in children with cancer from low- and middle-income countries. Level of abandonment of treatment among children with cancer ranged from 0% to 74.5%.[166] For acute lymphoblastic leukaemia, level of abandonment of treatment was greater in low-income countries (29%) than in upper-middle-income countries (2%), with wide

heterogeneity. They argued that prevention of abandonment of treatment is a priority and is as important as prevention of cancer treatment-related deaths or relapse in poor-resource settings. Abandonment of treatment was consistently under-reported and data were obtained only directly from authors.

In China, Shanghai is the only city that provides insurance for catastrophic diseases. At Shanghai Children's Medical Centre, during 1998–2003, out of 234 children diagnosed with acute lymphoblastic leukaemia, 66 abandoned treatment (mostly of them did not live in Shanghai), and 52 died due to treatment toxicity. According to one of the physicians of the Shanghai Medical Centre, the situation is much worse in other areas of the country, particularly in rural areas where only around 10% of Chinese children with acute lymphoblastic leukaemia receive protocol-based treatment.[167]

Twinning programmes: a real possibility for survival improvement among children with cancer in resource-poor countries

Twinning programmes are partnerships between public hospitals in developing countries and specialised cancer centres in the developed nations. By integrating education, capacity building and research, these programmes have been proved to be effective in decreasing deaths of children with cancer with long-term results. Successful established programmes include My Child Matters Initiative,[168] La Mascota programme,[169] the International Network for Cancer Treatment and Research,[170] and the International Outreach Programme (IOP).[171]

Howard et al.[115] described an example of the effectiveness of a twinning programme. They reviewed the outcomes of 375 children with acute lymphoblastic leukaemia treated in Recife, Brazil during 1980–2002, when a

partnership was developed through the International Outreach Programme. During 1980–1989 (early period), patients were treated at a public general hospital without a paediatric oncology unit, standardised treatment protocols, trained nurses or 24h physician coverage. Moreover, the availability of health supplies was limited. During 1990–1994 (middle period), children with acute lymphoblastic leukaemia were treated at a different hospital, with a protocol from the St. Jude Children's Research Hospital, but still without an oncology unit or specialised oncology nurses. During 1997–2002 (recent period), children with acute lymphoblastic leukaemia were treated with St. Jude protocol in a dedicated paediatric oncology unit, with trained health professionals and access to an Intensive Care Unit. Five-year event-free survival increased steadily: from 32% in the early period, to 47% in the middle period and 63% in the recent period. Abandonment of treatment decreased from 16% to 0.5%.

There is an enormous inequity in the distribution of resources allocated between countries for cancer care and control. Even though an estimated 80% of the disability-adjusted life-years (DALYs, i.e., a measure of overall disease burden expressed as the number of years lost due to ill-health, disability or early death) lost to cancer occur in low- and middle-income countries, only about 5% of the global resources for cancer are distributed to these countries. In Africa, this situation is even worse: Sub-Saharan African regions receive only 0.2% of global cancer spending.[172, 173] In paediatric oncology, survival is dreadful in those countries where the annual government expenditure on health is below US$200 per capita.[164]

In summary, in high-income countries, most children with cancer have access to care, and the main causes of treatment failure are relapse, drug

resistance and treatment toxicity. By contrast, in the low- and middle-income countries where 80% of children with cancer reside, access to care ranges from less than 10% to 70%, and the leading causes of therapy failure are abandonment of treatment and advanced disease at diagnosis, in addition to treatment-related toxicity and relapse. Currently, the main focus of leukaemia treatment in high-income countries is to find new therapeutic approaches to achieve cure, decrease toxicity and improve the quality of life of survivors. In contrast, in the low- and middle-income countries, the main focus of treatment is on improving access to optimal care and increasing the low outcomes. Table 3.5 summarizes these differences.

Table 3.5: Main differences in paediatric cancer care between high- and low- and middle-income countries. Adapted from a seminar by Ribeiro, RC; May 2013; www.cure4kids.org/ums/org.

Feature	High-income countries	Low- and middle-income countries
Access to care	Virtually 100%	<10% to 70%
Causes of failure	Disease relapse, drug resistance, treatment-related toxicity	Abandonment of treatment, advanced disease, treatment-related toxicity, relapse
Major focus on	Finding cures and improving quality of life of survivors	Improving access to care and increasing survival
Activities	Disease mechanisms (genomic medicine), risk-adapted therapy and prevent long-term complications	Understand the causes of abandonment of treatment, community education and adapt curative therapy with local resources

Survival is a measure of the cancer burden and the effectiveness of health systems, and plays a key role in the development of health policies. Long-term surveillance of cancer incidence has been essential to providing information on cancer aetiology and to help guiding cancer prevention policies. Surveillance of cancer survival is expected to be similarly valuable, allowing comparisons between and within countries and stimulating debate on strategies aimed at

reducing geographic and racial/ethnic survival inequalities, particularly in low- and middle-income countries.[174]

Along with data on incidence and mortality from cancer registries, survival trends provide a fundamental resource to help to interpret the influences of different risk factors, early diagnosis and treatment approach in different populations. Policy-makers paid little attention to population-based survival estimations until the publication of the EUROCARE studies.[175, 176] These studies compared survival from different types of cancer, in adults and children, across many countries in Europe, and focused on the reasons for the reported survival disparities. The findings of EUROCARE studies had a significant impact on cancer control policies in some countries such as United Kingdom and Denmark.

Moreover, the survival inequalities identified by the CONCORD study[20] have guide important political actions. For example, the very poor cancer survival observed in Algeria suggests deficiencies in the healthcare system and inappropriate cancer registration in the country. In the near future, cancer registries will be established in Algeria in order to improve monitoring of cancer incidence and survival.

In another report, Pritchard-Jones et al.[163] argued that, to improve access to care for children with cancer in low- and middle-income countries, each country should develop a national cancer control plan, taking into account socioeconomic, cultural and geographical factors. In addition, the authors emphasised the fundamental need for collaboration between national and international institutions in order to achieve sufficient recruitment of patients for clinical trials. This, eventually, can help further treatment developments.

In conclusion, the results of this literature review reinforce the need for

continuous global surveillance of paediatric and young adult cancer survival. Population-based comparisons of survival among children, adolescents and young adults with acute leukaemia can provide invaluable information to physicians, researches, policy-makers and governments. To effectively deliver health care to the population, it is necessary: (1) to assess the burden of disease in this population (e.g., cancer incidence and survival), (2) determine health care priorities, (3) implement health services, (4) monitor outcomes closely.

3.2 Acute myeloid leukaemia

3.2.1 Aims

The main aims of this literature review were to identify worldwide trends of survival and early death after childhood and young adult acute myeloid leukaemia and to investigate the main predictors of outcome.

3.2.2 Search strategy and eligibility criteria

In my previous literature review (section 3.1.2), I found that all relevant articles published in the LILACs and Global Health databases, were also published in English in Medline/PubMed. Therefore, I have not searched these databases for my second literature review. I searched PubMed and Scopus databases to identify studies reporting survival and early death after acute myeloid leukaemia in children, adolescents and young adults.

I initially searched for publications from the last 5 years (from 2009 onwards) but also included relevant studies cited in these publications. I used the following approach: 1) Study population: “Child*” OR “paediatric” OR “pediatric” OR “boys” OR “girls” OR “infant*” OR “baby” OR “babies” OR “adolescent*” OR

“young adult*” OR "AYA*” AND 2) Acute myeloid leukaemia terms: “acute” AND (“myeloid” OR “myeloblastic” OR “myelogenous” OR “promyelocytic” OR “non-lymphocytic” OR “non-lymphoblastic” OR “nonlymphocytic” OR “nonlymphoblastic”) AND “leukaemia” OR “leukemia” AND 3) Disease outcome terms: “survival” OR “early death” OR “treatment-related mortality” OR "early mortality” OR “premature death” OR “premature mortality” OR “induction death". No language restrictions were applied. After duplicates have been removed, all titles and abstracts of publications identified in the course of primary search were reviewed for relevance and eligibility criteria (full electronic search strategy is presented in Figure 3.4).

Eligibility criteria were: 1) original studies that report early death and any length of survival from acute myeloid leukaemia in children, adolescents and young adults 2) studies types were: cohort studies, clinical trials, reviews, systematic reviews and cross sectional studies. Conferences abstracts were excluded. Articles titles and abstracts were screened to select papers for full text screening.

3.2.3 Search results

My primary search identified 1,592 references. A total of 154 duplicates were removed using Endnote X6 and by hand searching, resulting in 1,438 references. From the remaining 1,438 references, 177 articles that appeared relevant from the abstract were reviewed in full and 39 were selected for inclusion in this literature review. Similar to the acute lymphoblastic leukaemia literature review, the studies covered many geographical areas, but most originated from Europe and the United States. These studies were further separated into two parts: 23

studies selected for the literature review on acute promyelocytic leukaemia (Table 3.8) and 16 studies for the literature review on non-APL acute myeloid leukaemia (Table 3.10).

The majority of these studies were clinical trials, but there were also several population-based studies. Some articles reported the results from all acute myeloid leukaemia subtypes combined, some studies report APL and non-APL AML findings separately and other studies excluded patients with acute promyelocytic leukaemia.

My search for early death after acute promyelocytic leukaemia was later expanded to report trends over a longer period of time (1990 onwards), following a suggestion made to me by a reviewer from *Cancer*, the peer-reviewed journal that accepted my paper for publication. Because the majority of these studies were clinical trials and used different eligibility criteria and definitions of early death, it was challenging to clearly compare population-level changes in early death over time, supporting the need for population-based studies to examine this question more closely.

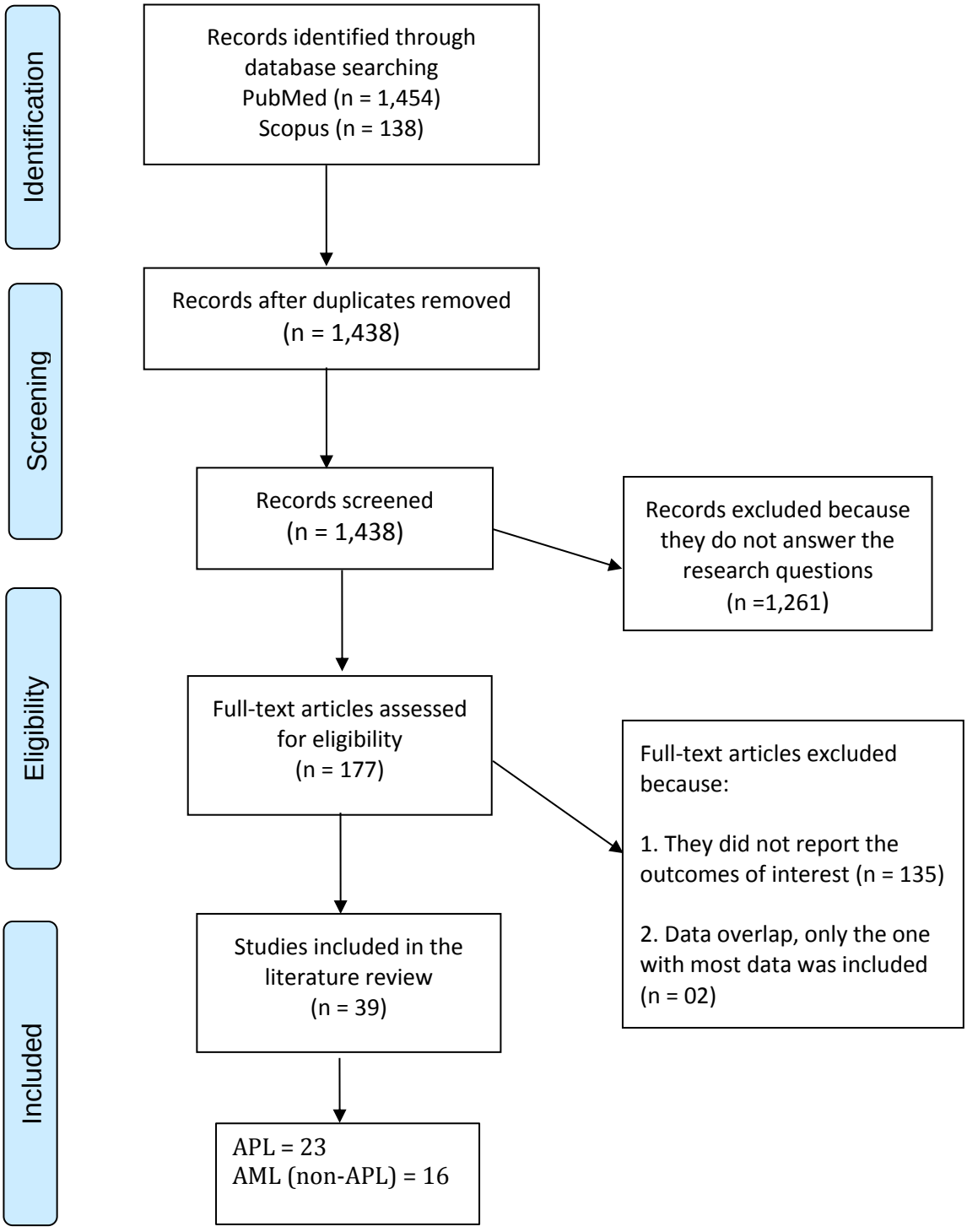

Figure 3.4: Process of selection of the studies for literature review on acute myeloid leukaemia

3.2.4 Main findings

3.2.4.1 Acute promyelocytic leukaemia

Acute promyelocytic leukaemia is a relatively rare haematologic neoplasm, characterised by an interruption of the myeloid differentiation at the promyelocytic stage. Even though its precise incidence is unknown, it is estimated that approximately 600 to 800 new cases per year occur in the United States,[177, 178] and accounts for about 4% to 8% of all acute myeloid leukaemias in children and adults.[179] Interestingly, the incidence of acute promyelocytic leukaemia is strongly associated with age. It is rare in children younger than 10 years, the incidence then increases continuously from 10 years until young adulthood, and remains constant up to 60 years when it starts to decline.[180, 181]

Intriguingly, the incidence of acute promyelocytic leukaemia is higher among Hispanics than non-Hispanic patients, with reports from Venezuela, Peru, Nicaragua, Spain, Brazil, and Mexico (Mexican Mestizos) confirming these findings.[178, 182-185] To date, no environmental or work-related factors have been associated with the incidence of this disease. Interestingly, the incidence of acute promyelocytic leukaemia is fairly similar in males and females, which differs from the gender distribution observed in other acute leukaemias (ALL and non-APL AML). However, one European study reported an unusually higher proportion of incident cases among females than males aged less than 40 years.[186]

In the mid-1970s, Rowley et al. discovered that a translocation between chromosomes 15 and 17 was associated with acute promyelocytic leukaemia.[187] This chromosome abnormality occurs in more than 90% of

acute promyelocytic leukaemia and is found exclusively in this malignancy.[178] This disease is genetically characterised by the presence of PML-RARα fusion protein, generated as a consequence of the specific reciprocal translocation of these chromosomes.[188] The PML-RARα fusion protein holds most of the functional domains of the PML and RARα proteins.[189] This discovery was fundamental in guiding molecular therapy for acute promyelocytic leukaemia. All-*trans* retinoic acid and arsenic trioxide have the potential to induce promyelocyte differentiation rather than their obliteration. These drugs have become the first example of differentiation induction treatment of human cancer.[28]

Hyperleukocytosis (100 X 10^9/L or greater) and coagulopathy are common features of acute promyelocytic leukaemia, often leading to early death, mainly due to intracranial haemorrhage.[190] Early death definition varies, according to different studies, as death occurring between 7 to 45 days after the diagnosis of acute leukaemia (Table 3.8). Most studies, however, define early death as death occurring within 30 days after leukaemia diagnosis, and this is the definition used in this thesis.

A characteristic of acute promyelocytic leukaemia is its exceptional responsiveness to all-*trans* retinoic acid (ATRA) or arsenic trioxide (ATO). Due to the severity of this disease with higher risk of bleeding, these drugs should be initiated as soon as acute promyelocytic leukaemia is suspected. No delay should occur waiting for laboratory confirmation.[191] The successful history of treatment for acute promyelocytic leukaemia is summarised in Table 3.6 and described below.

Table 3.6: The history of acute promyelocytic leukaemia: a paradigm of success in translational medicine. Adapted from Lo-Coco presentation at the Association des Médecins Hématologues et Oncologues du Québec (AMHOQ) Annual Meeting, 2013[192]

Year	Therapeutic advance
1957	First description of acute promyelocytic leukaemia (APL)
1973	APL is highly responsive to treatment with single anthracycline chemotherapy
1977	Specific chromosome translocation t(15;17) is identified
1987	APL is responsive to all-*trans* retinoic acid (ATRA)
1990	The altered genes are identified
1993	Clinical trials (AIDA study) show high cure rates with ATRA plus chemotherapy
1995	ATRA is approved by the US Food and Drug Administration in November
1996	APL is also responsive to arsenic trioxide (ATO)
2001	Registration and licensing of ATO for treatment of patients with relapsed APL
2004–06	High cure rates with ATRA plus chemotherapy
2006–12	It is possible to treat APL with ATRA + ATO (chemotherapy-free)

Survival and early death after acute promyelocytic leukaemia: results from clinical trials

Acute promyelocytic leukaemia was once a virtually fatal disease. In a retrospective study, 57 patients diagnosed with acute promyelocytic leukaemia during 1949–1964 were examined. Only 7% patients (n = 5) survived more than 4 months. The majority of patients died from haemorrhagic events.[193, 194]

During the 1970s and 1980s, several studies were performed that aimed at finding the best anti-haemorrhagic treatment for acute promyelocytic leukaemia, but no preventive or therapeutic regimen was found satisfactory. One retrospective study evaluated 268 consecutive patients aged 7 to 78 years from 29 Italian institutions during 1984–1987.[195] The goal of this study was to investigate the incidence of early haemorrhagic death and the effectiveness of different treatment approaches (heparin, anti-fibrinolytics or

supportive care alone). Overall, early haemorrhagic death was 9.4% and median survival was 12.5 months. The authors found no difference between the three treatment strategies and suggested that prospective randomized trials were urgently needed in order to identify better treatment for acute promyelocytic leukaemia and prevent haemorrhagic deaths.

In the 1990s and 2000s, several multi-collaborative clinical trials in Europe and the United States investigated the use of ATRA in newly diagnosed patients with acute promyelocytic leukaemia.[196-208] These studies have uniformly revealed that the introduction of ATRA alone or with chemotherapy decreased bleeding and, consequently, early death, improving overall survival. For instance, one study in the United States analysed 346 patients aged 1–81 years at diagnosis of acute promyelocytic leukaemia during 1992–1995. About half of patients received chemotherapy (control group) and half received ATRA. Overall, early death was 12.4%, with 11% occurring in the ATRA group and 14% in the chemotherapy group. Although the difference was not statistically significant (*P* = 0.52), the probability of relapse decreased in the ATRA group. Moreover, survival was significantly better in the ATRA group.[198]

Another study in Europe analysed 44 children aged 1–16 years when diagnosed with acute promyelocytic leukaemia during 1992–1997. Half of children received chemotherapy alone and the other half of children were treated with ATRA. Death within 6 weeks of diagnosis was 4.5% in the ATRA group vs. 32% in the chemotherapy group (*P* value = 0.04). Furthermore, overall survival was 87% in the ATRA group vs. 45% in the chemotherapy group (*P* value = 0.003).

Survival and early death after acute promyelocytic leukaemia: results from population-based studies

The outcomes reported from population-based studies are usually inferior to those described in clinical trials or single institutions in the developed countries. The main reason for this is that population-based studies provide data on virtually all patients diagnosed with leukaemia (or other type of cancer) in the population. Differently, clinical trials include selected groups of patients, usually excluding those who are very sick and may not tolerate intensive treatment protocols. Therefore, while in developed countries early death has been reported to be around 3% to 8% in clinical trials,[9, 209] results from population-based studies in Europe (Sweden Cancer Registry) and in the US (SEER data) has varied from 17%–29%.[22, 186, 210] These findings caused some controversy in the literature, on whether early death after acute promyelocytic leukaemia has decreased after the introduction of ATRA. Some examples are described below.

Derolf et al.[210] estimated survival and early death of 111 patients with acute promyelocytic leukaemia (corresponding to 2.5% of all cases of acute myeloid leukaemia) aged 0 to > 80 years, during 1993–2005, using data from the nationwide Swedish Cancer Registry. Early death (30-day mortality) decrease from 27% in 1993–1999 to 18% in 2000–2005 and 3-year relative survival was 53% vs. 69% respectively. The authors suggested that the introduction of ATRA in the treatment of this leukaemia might have contributed to the better outcomes in the more recent calendar period.

Lehmann et al.[186] studied 105 patients aged 16 years or older, with acute promyelocytic leukaemia (3.2% of all acute myeloid leukaemia cases)

during 1997–2006, using data from the Swedish Adult Acute Leukaemia Registry. This Registry works in collaboration with the Regional Tumour Registry in the six Swedish health care regions, reporting 98% of coverage of all acute leukaemia patients. In contrast to the previous study, the authors have not observed improvement in early death and reported early death as high as 29%. Strikingly, they found that 35% of patients had not received ATRA and about 41% of early death was secondary to haemorrhage. In addition, the authors observed that early death increased with age at diagnosis, and was strongly associated with poor performance status (PS classification is described in Table 3.7). They concluded that, at a population level (unselected patients), early death is still remarkably high in Sweden and suggested that lack of adherence to treatment guidelines may have contributed to this unfavourable outcome.

Table 3.7: Performance Status Classification. Source: The World Health Organisation / Eastern Cooperative Oncology Group Performance Status[211, 212]

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

In the United States, Park et al.[22] examined 1,400 children and adults with acute promyelocytic leukaemia during 1992–2007 using SEER data. Overall early death was 17.3%, with only a slight change over time (from

22.3% in 1992–1995 to 14.7% in 1996–2001 and 17.5% in 2002–2007, *P* value = 0.068). The authors concluded that early death remains high in the United States and highlighted that health care providers should be educated to recognise acute promyelocytic leukaemia as an emergency and promptly initiate ATRA.

Finally, a recent study in the United States[213] reported the results from a population-based study using SEER data from 1977–2007 and a hospital-based study conducted during 1997–2009 that examined early death after promyelocytic leukaemia in patients aged 15 years or older. The authors found high 30-day mortality in both studies (26% and 20% respectively). Seven-day mortality was also examined in the hospital data and was found as high as 19%. Ten out of 13 patients who died within 30-days in the later study received ATRA. This study emphasised that early death is currently the greatest contributor to overall mortality in patients with acute promyelocytic leukaemia despite the use of ATRA. They argue that further understanding of the pathogenesis of haemorrhagic complications in acute promyelocytic leukaemia and use of more aggressive supportive care are warranted.

Differentiation syndrome

Although bleeding is the major cause of early death in children and adults with acute promyelocytic leukaemia, other relevant causes of death are infections and differentiation syndrome, complications that often occur in the first 3 weeks of treatment.[214] Differentiation syndrome is a relatively common and serious complication secondary to the use of ATRA and/or arsenic trioxide for the treatment of acute promyelocytic leukaemia. This syndrome is estimated

to occur in 2 to 31% patients during induction treatment and is characterised by fever and pulmonary, cardiovascular, and/or renal dysfunction. Its pathogenesis is not entirely clear but it seems to be secondary to an inflammatory systemic response caused by ATRA (or arsenic) use. Due to the severity of this syndrome, several collaborative groups have incorporated the use of corticosteroids as preventive and therapeutic measures. Treatment is essentially supportive and may include vasopressors, mechanical ventilation and dialysis. In critical patients, ATRA and arsenic should be temporarily discontinued and the patients admitted to an Intensive Care Unit.[215, 216]

Acute promyelocytic leukaemia in developing countries

Despite the excellent prognosis of acute promyelocytic leukaemia among children and adults, the success of new contemporaneous therapeutic regimens has not been equally shared in low- and middle-income countries. In Brazil, a retrospective study[217] with 134 patients aged 5–79 years during 2003–2006, revealed that only 68% of patients treated with anthracyclines and ATRA reached complete remission. Thirty-two percent of patients died during induction therapy and about 10% died during the consolidation phase, numbers significantly higher than those reported in high-income countries (5%–10% during induction and less that 5% during consolidation).[9, 218, 219] Early death (defined in this study as death within 14 days of diagnosis) was very high (26.4%) and haemorrhage was the main cause of death (22%). The authors concluded that the highest priority to improve outcome in developing countries might be intensive treatment and supportive care during the induction phase, when the majority of haemorrhagic deaths occur. They

highlighted that no patient was excluded from the study based on their age or unfavourable performance status (differently than what usually occurs in clinical trials). This study also suggests that the availability of ATRA and anthracyclines itself is not enough to decrease the gap in outcome between developed and developing countries.

The International Consortium on Acute Promyelocytic Leukaemia

Over a decade ago, a group comprised of international members of the American Society of Haematology developed an initiative to help developing countries to improve outcomes from acute promyelocytic leukaemia through medical education programmes.[220] The International Consortium on Acute Promyelocytic Leukaemia was created in 2005 and received support from collaborative groups in the United States and Europe. The goal of this consortium is to develop treatment guidelines based on successful trials conducted in the developed countries, but adapted to local conditions. This Consortium offers online meetings with experts (usually twice a month), helps in the development of therapeutic protocols, and monitors the supportive care provided and treatment response. This initiative has allowed some patients with acute promyelocytic leukaemia in countries such as Brazil, Mexico, Chile and Uruguay to achieve outcomes similar to those in high-income countries.[220]

In summary, acute promyelocytic leukaemia is currently a highly curable disease. With modern treatment that includes chemotherapy with anthracyclines-based agents and ATRA (or arsenic trioxide), many large collaborative trials in Europe, the United States and Japan have reported

complete remission rates up to 95%, and cure in 80% or more patients treated with these regimens.[9, 186, 196, 197, 199, 200, 209] Nevertheless, there is evidence from both population-based studies and also from clinical trials that early death remains high in some centres in developed and especially in the developing countries. Further evaluation of early death trends at the population level and examination of predictors of early death are needed.

Table 3.8: Consecutive reports on early death and survival in patients diagnosed with acute promyelocytic leukaemia, 1990–2014

First author, year, setting	Study design	N	Period	Age (Years)	Early death		Survival
					Definition	Percentage	
1.Rodeghiero F, 1990, Italy[195]	Clinical trials	268	1984–1987	7–78	Death occurring in the first 10 days after starting chemotherapy	9.4% died due to haemorrhagic events and 3.2% due to other causes (pre-ATRA era)	Median survival: 12.5 months for all patients (pre-ATRA era)
2. Fenaux P, 1993, Europe[196]	Clinical trials	101	1991–1992	6–67	Death during chemotherapy or ATRA, or during the period of aplasia after chemotherapy, without evidence of resistant leukaemia	9.0% in the ATRA group and 8.0% in the chemotherapy group	1-y overall survival: 91% (ATRA group) 80% (chemotherapy only)
3. Estey E, 1997, US[197]	Clinical trial	ATRA: 43 Control: 57	1991–1995 1979–1991	13–72 17–80	Death during induction therapy	19.0% 30.0%	1-y disease-free survival: 87% (ATRA group) 67% (control group)
4. Tallman MS, 1997, US[198]	Clinical trials	346	1992–1995	1–81	Death within 28 days of diagnosis	12.4% (overall) 11.0% (ATRA group) 14.0% (control group)	1-, 2- and 3-y overall survival respectively: 84%, 74% and 71% (ATRA group) 75%, 57% and 50% (control group)
5. Mandelli F, 1997, Europe[199]	Clinical trials	240	1993–1996	2–73	Death during induction therapy	5.0%	1- and 2-y overall survival respectively 90% and 87% (ATRA + chemotherapy)
6. Fenaux P, 1999, Europe[200]	Clinical trials	439	1993–1996	≤ 77	Death occurring during induction treatment with ATRA, without evidence of resistant leukaemia	7.0%	2-y overall survival: 84% (ATRA followed by chemotherapy) 81% (ATRA + chemotherapy)
7. Sanz MA, 1999, Spain[201]	Clinical trials	123	1996–1998	1–74	Death occurring during induction therapy or during the period of aplasia after chemotherapy	9.8%	2-y overall survival: 82% (ATRA + chemotherapy)
8. Di Bona E, 2000, Italy[202]	Clinical trials	622	1989–1997	1–74	Early haemorrhagic deaths occurring in the first 10 days after starting treatment	3.8% in study w/ idarubicin + ATRA, 7.3% w/ idarubicin alone	N/A
9. Lengfelder E, 2000, Europe[203]	Clinical trials	51	1994–1999	16–60	Death during induction therapy before recovery from therapy immunosuppression	8.0%	2-y overall survival: 88% (ATRA + chemotherapy)
10. Mann G, 2001, Austria[204]	Clinical trials	44	1993–2002	1–16	Death within 6 weeks of diagnosis	4.5% (ATRA group) 32.0% (control group)	5-y overall survival: 87% (ATRA + chemotherapy) 45% (chemotherapy only)
11. Asou N, 2001, Japan[205]	Clinical trials	369	1992–1997	15–86	Death within 28 days of start of chemotherapy	8.0%	6-y overall survival: 65% (ATRA alone or with chemotherapy)
12. Testi AM, 2005, Italy[206]	Clinical trials	107	1993–2000	1–17	Death occurring within 34 days of diagnosis	3.7%	10-y overall survival: 89% (ATRA + chemotherapy)

First author, year, setting	Study design	N	Period	Age (Years)	Early death		Survival
					Definition	Percentage	
13. Schlenk RF, 2005, Europe[221]	Clinical trials	82	1995–2003	16–60	Death <7 days after completion of the first induction therapy or death during double induction therapy	12%	Overall survival at 46 months: 82% (ATRA + chemotherapy)
14. Yanada M, 2007, Japan[208]	Clinical trial	279	1997–2002	15–70	Early haemorrhagic death	3.2% (ATRA for all patients)	5-y event-free survival 68% in patients without haemorrhage event 31% in patients with haemorrhage event
15. Jacomo RH, 2007, Brazil[217]	Hospital-based (12 institutions)	134	2003–2006	5–79	Early mortality: death within 14 days of diagnosis. Death during induction Death during consolidation.	26.4% 32.1% 10.5%	Mean survival time = 707 days (583–820). 3-year overall survival <60% (Anthracyclines + ATRA)
16. Derolf AG, 2009, Sweden[210]	Population-based	111	1993–2005	All ages included	Death occurring within 30 days of diagnosis. Induction mortality	27% during 1993–1999 18% during 2000–2005	3-y relative survival: 61% during 1993–1999 69% during 2000–2005
17. Lo-Coco F, 2010, Italy[9]	Clinical trials	642 453	1993–2000 2000–2006	18–≤ 61	Induction death – death within 45 days of treatment using ATRA and idarubicin	5.5% for AIDA-0493[1] 5.6% for AIDA-2000[2]	6-y overall survival 78.1% for AIDA-0493[1] 87.4% for AIDA-2000[2]
18. Lehmann S, 2011, Sweden[186]	Population-based	105	1997–2006	≥16	Death within 30 days of diagnosis	29.0% (35.0% of patients did not receive ATRA)	5-y overall survival: >16y and <40y = 82%; 40y–59y = 75%; ≥ 60y = 25%
19. Park JH, 2011, US (SEER)[22]	Population-based	1,400	1992–2007	All ages	Death within 30 days of diagnosis	17.3%	3-y overall survival: 70%
20. Iland HJ, 2012, Australia and New Zealand[209]	Clinical trials	124	2004–2009	>1	Induction death within 36 days of ATRA exposure	3.2%	2-y overall survival: 93%
21. McClellan JS, 2012, US (Stanford and SEER)[213]	Hospital-based & population-base	70 N/A	1997–2009 1977–2007	≥15	Death within 7 or 30 days from the start of chemotherapy	18.6% (7 days) and 26.0% (30 days) 20.0% (30 days)	3-y overall survival of high-, intermediate- and low-risk patients were 56%, 70% and 83%, respectively (Stanford)
22. Altman JK, 2013, Israel and US[222]	Hospital-based	204	1992–2009	1–85	Death occurring within 30 days of presentation to medical care	11.0%, 61% due to haemorrhage (only in 31% of cases ATRA was ordered the day PL was suspected)	N/A
23. Fisher BT, 2014, US[21]	Hospital-based	163	1999–2009	All ages Included	Induction death within 7 and 30 days of admission	4.3% (7 days) 6.1% (30 days)	N/A
Abbreviations: ATRA, all-*trans* retinoic acid; N/A, not applicable; SEER, Surveillance Epidemiology and End Results; US, United States; AIDA, Amsterdam Investigator-initiate D Absorb trials							

3.2.4.2 Acute myeloid leukaemia

Acute myeloid leukaemia is the most common type of acute leukaemia and its incidence increases with advanced age. It accounts for about 15%–20% of all leukaemias in children, approximately 33% of leukaemia in adolescents and 50% of leukaemia in adults.[51]

Similarly to acute lymphoblastic leukaemia, the incidence of non-APL acute myeloid leukaemia is higher among males than females with a ratio of 1.5:1. The aetiology of acute myeloid leukaemia remains largely unknown. The most recognised cause of this malignancy is previous treatment with chemotherapy or radiation, leading to 10%–20% of cases of acute myeloid leukaemia cases.[178, 223]

Patients with non-APL acute myeloid leukaemia continue to have a much lower long-term survival compared to those with acute lymphoblastic or promyelocytic leukaemia. Biologic and non-biologic factors predictive of outcome after acute myeloid leukaemia are described below.

Survival trends and the effect of age at diagnosis on the outcome of acute myeloid leukaemia in children, adolescents and young adults.

Several studies have shown improvement in survival after acute myeloid leukaemia over time, but to a lesser degree when comparing with the survival from acute lymphoblastic and promyelocytic leukaemias. Pulte et al.[224] investigated 5- and 10-year survival of 560 children aged 0–14 years with acute non-lymphoblastic leukaemia and also 2,855 children with acute lymphoblastic leukaemia during 1990–2004. This study showed that 5-year relative survival improved from 41.9% in 1990–1994 to 59.9% over 2000–

2004 among patients with non-lymphoblastic leukaemia, while 5-year survival for acute lymphoblastic leukaemia increased from 80.2% to 87.5% in the same period.

In another study, Pulte et al.[10] examined 5- and 10-year survival of adolescents and young adults with haematologic malignancies. The authors examined 709 patients aged 15–24 years with acute myeloid leukaemia during 1985–2005. Survival improved considerably but it was lower than that of the younger paediatric cohort. Five-year relative survival improved from 20.0% in 1981–85 to 47.2% in 2001–2005, while 10-year survival increased from 15.2% to 45.1%. The authors hypothesized that the lower survival in these older patients may be due to the lack of insurance, inferior enrolment in clinical trials and lower adherence to treatment.

In Sweden, a large study[210] (n = 9,729) was conducted to examine the survival trends after acute myeloid leukaemia in all patients registered in the Swedish Cancer Registry, during a long period of time (1975–2005). Although this study has included patients with a previous malignancy (which may result in worse outcomes), survival after acute myeloid leukaemia was found higher than that observed by Pulte et al. in the two studies mentioned above. Five-year relative survival in the more recent era of treatment (1997–2005) was 65% for patients aged 0–18 years and 58% for those aged 19–40 years. The authors suggested that the superior survival of patients with acute myeloid leukaemia in Sweden compared with that in the United States might be to the public health system that guarantees equal access to health service for all citizens. In Sweden, virtually all patients are treated at non-private hospitals with haematologic units and therefore have access to optimal treatment,

including haematopoietic stem cell transplantation, without financial burden for their families.

Other researchers have also investigated the association of age at diagnosis with outcome after acute myeloid leukaemia. Razzouk et al.[225] analysed 424 patients aged 0–21 years from two American institutions during 1983–2002. Patients with Down syndrome and acute promyelocytic leukaemias were excluded due to their distinctive (better) prognosis compared with other subtypes of acute myeloid leukaemia. This study revealed that, after adjusting for cytogenetic characteristics and white blood cell count, patients aged less than 10 years of age at diagnosis had higher 5-year overall survival (49.4%) than those aged 10 years or older (34.8%). The authors found that the hazard of death increased substantially with each year of age in both calendar periods examined (1983–1989 and 1990–2002). They concluded that older patients (≥ 10 years) do not benefit, to the same extent younger patients do, from the use of modern intensive treatment, including haematopoietic stem cell transplantation. They suggested that further research is required to evaluate if pharmacokinetic differences play a role on the higher rate of treatment-related mortality among patients aged 10 years or older.

An European study[51] evaluated 891 children aged under 18 years during 1993–1998 treated in the AML BMF trials and 290 adolescents and young adults aged 17 to 29 years in the AML Cooperative Group (AMLCG) and AML Study Group (AMLSG) trials during 1992–1999. Five-year event-free survival was higher for younger than older patients: 54%, 46% and 28% for patients aged 2–12 years (children), 13–20 years (adolescents) and 21–29

years (young adults), respectively. When patients with favourable karyotypes were excluded, 5-year event-free survival was similar for infants (< 2years) and children (44% and 46% respectively) and lower for adolescents and young adults (35% and 23%, respectively). The authors concluded that the prognosis of acute myeloid leukaemia decreases after childhood regardless of other risk factors such as karyotype.

Walter et al.[226] investigated early death during induction therapy (death occurring within 28 days after initiation of treatment) in 3,365 older patients (aged 17–89 years) enrolled in clinical trials in the United States during 1986–2009. Overall early death was 10.3% (11.1% at Southwest Oncology Group and 9.9% at MD Anderson Cancer Center clinical trials). The authors examined the association between early death and age and other covariates. These covariates were: platelets, white blood cell count, albumin, creatinine, bilirubin, percentage of blasts in the peripheral blood and bone marrow, haemoglobin, fibrinogen, lactate dehydrogenase, blood neutrophils, as well as sex, race, performance status and secondary AML. Performance status was the strongest single predictor of early death (or treatment-related mortality). The authors concluded that, even though age does increase the risk of treatment-related complications and death, it should not be used as a single predictor of outcome to guide therapy (usually set to an arbitrary cut-off of 55-60 years that separates younger and older patients).

More recently, Rubnitz et al.[227] evaluated the effect of age on outcome for children and young adults with acute myeloid leukaemia treated with different protocols. They examined 351 patients aged 0–21 years treated in 3 consecutive clinical trials at St. Jude during 1991–2008. Using the most

recent protocol (AML02: 2002–2008), the authors found a substantial increase in survival for older patients (10–21 years), with 3-year overall survival currently similar to that for younger patients (0–9 years): 69% vs. 75%, respectively (*P* value = 0.36). This result differs from those of previous population-based studies[6] and clinical trials (including one in the same institution[225]) performed between 1980s and 1990s. The authors suggested that the survival improvement observed for all ages is secondary to the use of target therapy, aggressive supportive care and monitoring of minimal residual disease. Nonetheless, the cumulative incidence of treatment-related mortality was significantly higher for patients aged 10–21 years than that for younger children. They concluded that treatment toxicity remains an important problem for adolescents and young adults with acute myeloid leukaemia and re-emphasised the prognostic significance of age on outcome.

The association of race and ethnicity on outcome of children and young adults with acute myeloid leukaemia

There is evidence that race/ethnicity is also associated with the outcome of children, adolescents and young adults with acute myeloid leukaemia. A population-based study[228] evaluated the effect of race and insurance in the outcome of 523 patients aged 21–64 years with acute myeloid leukaemia diagnosed during 1999–2006 in the State of Virginia, United States. The results of this study revealed that the hazard of death for black patients was increased by 43% relative to that for white patients (HR = 1.43). Moreover, uninsured and publicly insured patients also had a higher hazard of death compared to privately insured patients (HR = 1.29 and 1.39, respectively),

suggesting the need for better insurance coverage of minority and disadvantage group of patients. The authors also highlighted the results of previous studies showing that black patients are more likely to be diagnosed with disease in more advanced stages and receive sub-optimal treatment.

A more recent study[229] using SEER data from 1992–2006, examined the association of race/ethnicity on outcome of patients aged ≥ 15 years with acute leukaemia and other types of cancer. This study demonstrated that 5-year survival has improved over time for all types of malignancies. For acute leukaemia, survival increased substantially for non-Hispanic white and younger (less than 65 years) Hispanic patients, but here was no survival improvement for black and older Hispanic patients. In fact, there was evidence that survival inequalities increased between non-Hispanic white and black patients during the two calendar periods examined. Five-year survival for patients aged 15–64 years, diagnosed with acute leukaemia during 1992–1996 and 2002–2006 was respectively: 28% and 39% for non-Hispanic white, 29% and 38% for Hispanic and 26% and 27% for black patients.

Rubnitz et al.[230] studied 229 white and 58 black patients aged 21 years or younger diagnosed with acute myeloid leukaemia during 1980–2002 and enrolled in five consecutive clinical trials at St. Jude Children's Research Hospital. Although the authors did not find a difference in survival between white and black children over the entire study period, they did observe worse survival for black children in the more recent trial: 5-year overall survival for black children was 27% vs. 56% for white children. However, these results did not reach statistical significance, possibly due to the inferior power to detect differences when data from an individual trial were examined separately

compared to data from the combined trials. The authors argued that the trend toward worse outcome for black children might be due to pharmacogenetic differences that may influence their response to targeted therapy. In addition, Hispanic children treated at St Jude (n = 34) seemed to have a good outcome: 5-year overall survival was 67% for all trials combined and 75% during the most recent trial (1997–2002). The authors suggest that these results reflect the favourable leukaemia characteristics of these patients: the majority was younger than 10 years and had approximately 43% of favourable cytogenetic abnormalities.

Non-biological factors associated with survival of children, adolescents and young adults with acute myeloid leukaemia

Borate et al.[231] studied the association between non-biological factors (i.e. health insurance status, marital status and income) and survival among patients aged 19–64 years when diagnosed with acute myeloid leukaemia. They examined 5,541 patients during 2007–2011 using SEER 18 data. The results of this study showed worse survival for single or divorced patients, those with no insurance or public health insurance, and among patients who live in a county within the lower quintiles of median household income, compared with married, privately insured patients and those living within the higher two quintiles of median household income.

Another European study[232] investigated the association between socioeconomic status and outcome after acute myeloid leukaemia and multiple myeloma. A total of 5,541 patients of all ages, diagnosed with acute myeloid leukaemia during a 33-year period (1973–2003) were examined. The

authors used occupation as a surrogate for socioeconomic status and found that patients with higher than lower socioeconomic status had better survival. The overall mortality was higher among blue-collar workers compared with white-collar workers in the three calendar periods examined: HR of death was 1.26, 1.23 and 1.45 during 1980–1989, 1990–1999 and 2000–2005, respectively.

Cytogenetic alterations effect on outcome after acute myeloid leukaemia

Cytogenetic alterations are considered one of the most relevant prognostic factors in acute myeloid leukaemia. Grimwade et al.[233] studied 1,612 patients aged 0–55 years with de novo and secondary acute myeloid leukaemia during 1988–1995 in the United Kingdom. The main aim of this study was to evaluate the significance of pre-treatment diagnostic cytogenetics on outcome of patients with acute myeloid leukaemia. The authors identified groups of children and young adults that present different responses to treatment and relapse risk, allowing for targeted therapy. In addition, the cytogenetic risk groups were found to have significant predictive value for the outcome of haematopoietic stem cell transplantation. Nonetheless, cytogenetic analysis was not able to precisely predict outcomes for individual patients, mainly for those within the heterogeneous intermediate risk group. The authors highlighted the need of further identification of independent prognostic factors, including molecular features, to better guide therapy and improve outcome after acute myeloid leukaemia. The survival of children and young adults in this cohort varied widely according to the cytogenetic risk: 5-year overall survival was 65%, 41% and 14% for favourable, intermediate and adverse risk

groups, respectively. Table 3.9 shows the cytogenetic risk groups for acute myeloid leukaemia.

Table 3.9: Cytogenetic Risk Group. Source: Grimwade et al., Blood 1989[233]

Risk Group	Cytogenetic abnormality	Additional comments
Favourable	t(8;21) t(15;17) inv(16)	Alone or in conjunction of other abnormalities
Intermediate	Normal +8 +21 +22 del(7q) Del(9q) Abnormal 11q23 All other structural/numerical abnormalities	Cytogenetic abnormalities not classified as favourable or adverse Lack of additional favourable or adverse cytogenetic changes
Adverse	–5 –7 del(5q) Abnormal 3q Complex	Alone or in conjunction with intermediate-risk or other adverse-risk abnormalities

The impact of molecular alterations on survival after acute myeloid leukaemia

In the last two decades, various studies have been conducted in order to identify potential molecular targets to guide new therapeutic approaches and increase survival after acute myeloid leukaemia in children and adults. Ho et al.[234] evaluated a total of 847 patients aged 1 month to 20 years, who were enrolled in the Children's Oncology Group collaborative clinical trials during 1995–2005. Thirty-eight (4.5%) patients had *CEBPA* mutation, which is recognised to be associated with leukaemia outcome. There were two types of *CEBPA* mutations more often associated with older patients and those with normal karyotype. The *CEBPA* mutations have occurred exclusively in intermediate risk patients and were considered an independent predictive

factor of outcome after acute myeloid leukaemia. Patients with single or double *CEBPA* mutations have favourable outcomes with lower incidence of relapse (13% vs. 44%) and higher survival (83% vs. 51%) than those without *CEBPA* mutations. The authors concluded that patients with *CEBPA* mutations may not benefit from haematopoietic stem cell transplantation in first remission and should be treated with chemotherapy alone.

One European study[235] analysed the prognostic significance of cytogenetic abnormalities in 729 children aged 0–16 years enrolled in the UK Medical Research Council trials (AML 10 and 12), during 1988–2002. The most common alteration was rearrangements of 11q23 found in about 16% of patients with acute myeloid leukaemia (half of them were infants). This study confirmed the favourable prognosis of the cytogenetic abnormalities t(8;21) and inv(16) with 10-year survival equal to 80% and 81%, respectively. The poor prognosis abnormalities with correspondent 10-year overall survival (OS) were: abnormality of 12q, 35%; t(6;9), 50%; abnormality of 5q, 27%; monosomy 7, 32%; and t(9;22), survival not estimated due to small number of cases. The 10-year overall survival for children with normal karyotype was 58%. The authors highlighted that the predictive significance of these alterations may be different in the future, and further studies should be done to identify new genetic alterations that may guide novel risk stratification for acute myeloid leukaemia.

In summary, in order to improve survival, there is a need to integrate basic sciences with clinical sciences (translational medicine), which includes genome-wide analysis for every patient with acute myeloid leukaemia in order to identify novels molecular markers that have prognostic implications.

The importance of population-based studies for acute myeloid leukaemia

A study in Sweden[236] discussed the significance of population-based data on the advance of acute myeloid leukaemia. The nationwide Swedish Cancer Registry is a well-recognised registry for its high-quality and comprehensive source of information on individual cancer patients. Reporting is compulsory in Sweden, thus the registry collects information on essentially all patients with cancer in the country. In addition to the routinely collected data, there is information on patients' eligibility for chemotherapy, performance status (available for approximately 97% of cases) and nearly complete follow-up of patients. Furthermore, because all Swedish citizens have a unique personal identification code, all their information, including level of education, medical history and cause of death can be tracked after migration within its territory and upon return from overseas. It is also possible to evaluate socioeconomic status based on national registries. The authors of this study assert that population-based data are important not only to provide incidence and mortality trends, but also relevant supplementary information for clinicians to guide therapeutic decisions. Using data from the Swedish Acute Leukaemia Registry during 1997–2007, more than 3,000 patients aged 16 years or older with acute myeloid leukaemia were examined. The authors investigated the effect of selecting patients with acute myeloid leukaemia and better performance status on survival. Early death (30-day mortality) after acute promyelocytic leukaemia was also investigated. The main findings are described as follows:

1. Five-year overall survival for non-APL AML patients was 60% for patients aged less than 30 years, 49% for those aged 30–44 years and, for patients older than 54 years no more than 23%. When only patients with performance status 0–II were included in the analysis, survival increased substantially, mainly for patients aged 55 years or more (about a 50% increase).

2. Overall early death after acute promyelocytic leukaemia was 42% during the late 1990s. For patients younger than 60 years, early death declined from 25% in the late 1990s to 10% from 2001 onwards. The authors concluded clinical trials continue to be the best study design to investigate specific therapeutic approaches for acute leukaemias. However, important limitations exist due to small number of patients with specific subtypes of disease, and selection of patients. The authors emphasized the importance of linking high-quality cancer registry data with patient information from medical records for the improvement of cancer outcome.

Haematopoietic stem cell transplantation and acute myeloid leukaemia

Haematopoietic stem cell transplantation (HSCT) is an established curative therapeutic possibility for a minority of high-risk patients with acute myeloid leukaemia. In the last 10 years, the use of HSCT has increased in the developed countries. This is, in part, due to an increase in the use of unrelated donor, better supportive care and the availability of less toxic pre-treatment regimes.[237-239] However, the indication of HSCT remains somewhat controversial. The major causes of HSCT failure are relapse and treatment-related toxicity, including graft-versus-host disease, chemotherapy and

radiation toxicity, and severe infections. Therefore, a key strategy is to focus on strategies to prevent post-transplant relapse.

Various factors should be accounted for when using genetic data to recommend HSCT to a patient with acute myeloid leukaemia. For instance, although the presence of *NPM*1 gene mutation has been considered to have a "protective" effect for patients with AML, this may not be true for patients older than 65 years according to the results of a recent clinical trial.[240] A better understanding of the biology of acute myeloid leukaemia has allowed an improved pre-, peri- and post-transplant management. This has been enabled by the use of less toxic drugs. The combination of monoclonal antibodies with classical drugs are promising and may allow intensive treatment without increasing treatment related-toxicity.[237]

In conclusion, acute myeloid leukaemia is a very complex malignancy characterised by phenotypic, cytogenetic, and genetic heterogeneity. Its aetiology is largely unknown, but may occur due to a preceding haematological disorder or exposure to toxic agents such as chemotherapy drugs. It is accepted that nearly all patients with acute myeloid leukaemia have multiple malignant clones. Each subclone comprises a unique combination of genetic and epigenetic alterations and may have different responses to treatment.[241]

Biological and non-biological factors such as socioeconomic status, race/ethnicity, marital status, and genetic and epigenetic characteristics have been implicated in outcomes from acute myeloid leukaemia. Age at diagnosis remains one of the most relevant prognostic factors for acute myeloid leukaemia along with performance status.

As documented in this literature review, improvement in survival from acute myeloid leukaemia has been modest, particularly when compared with other types of acute leukaemias. Treatment relies mostly on chemotherapy, appropriate use of bone marrow transplant and aggressive supportive care. The current consensus is that the better approach to treat these patients will rely on individualised treatment strategies (precision medicine), but additional research is needed to identify the best treatment for each patient.

Table 3.10: Characteristics of included studies and results of the literature review on acute myeloid leukaemia

First Author, Year, setting	Study design	Period	Age at diagnosis (Years)	Number of cases	Early death		Survival or hazard of death
					Definition	Percentage	
1. Grimwade D, 1998, UK[233]	Clinical trials (MRC AML 10)	1988–1995	0–55	1,612 with de novo or secondary AML	N/A	N/A	5-y OS by cytogenetic risk: 65%, 41%, 14% for favourable, intermediate and adverse risk, respectively
2. Razzouk BI, 2006, US[225]	Clinical trials (2 institutions)	1983–2002	< 21	St. Jude: 288 MDA: 136	N/A	N/A	Children w/AML (non-APL, non-DS) aged <10y has better outcome w/ the more recent intensive treatment: 5-y OS = 49.4% (<10y) and 34.8% (age ≥ 10y)
3. Rubnitz JE, 2007, US[230]	Clinical trials	1980–2002	≤ 21	White: 229 Black: 58	N/A	N/A	5-y OS was 39% for whites and 34% for blacks. Trial AML97: 56% whites and 27% blacks
4. Creutzig U, 2008, Europe[51]	Clinical trials	1993–1998 1992–1999 1993–1998	<18 17–29	AML BMF: 891 AMLCG and AMLSG: 290	N/A	N/A	5-y EFS: 54% (2 to 12y), 46% (13 to 20y) and 28% (21 to 29y). Excluding patients w/ favourable karyotype: same results for children (44%) and infants (46%), and inferior for adolescents (35%) and young adults (23%)
5. Pulte D, 2008, US (SEER)[224]	Population-based	1990–2004	0–14	NALL: 560	N/A	N/A	5- and 10-y relative survival improved from 1990–94 to 2000–04 from 41.9% to 59.9% and from 38.7% to 59.1%, respectively
6. Pulte D, 2009, US, SEER[10]	Population-based	1985–2005	15–24	AML: 709	N/A	N/A	5- and 10-y survival improved from 1981–85 to 2001–05 from 20.0% to 47.2% and from15.2% to 45.1%, respectively
7. Derolf AR, 2009, Sweden[210]	Population-based	1973–2005	All age included	9,729	N/A	N/A	5-y RS in 1997–05 was 65 % for patients aged 0–18y and 58% for 19–40y. Excess mortality when MDS preceded AML (HR=1.51)
8. HO PA, 2009, US[234]	Clinical trials	1995–2005	1mo to <21y	847	N/A	N/A	*CEBPA* mutations in 4.5% of patients (mostly older and w/ normal karyotype), exclusively in intermediate cytogenetic risk. 5-y OS for patients w/ vs. without *CEBPA* = 83% and 51%
9. Kristinsson, 2009, Sweden[232]	Population-based	1973–2005	All aged included	9,165	N/A	N/A	Occupation was a proxy for SES. Patients with higher than lower SES had better survival. Overall mortality was higher among blue-collar workers compared with white-collar workers in the 3 calendar periods: HR= 1.26, 1.23 and 1.45 during 1980–1989, 1990–1999 and 2000–2005, respectively).
10. Harrison CJ, 2010, UK[235]	Clinical trials	AML10: 1988–95 AML12: 1994–02	0–16	729 (non-APL)	N/A	N/A	10-y OS for children w/ normal karyotype = 58% vs. w/ t(8;21) = 80%; w/ inv(16) = 81% w/ 12q abnormalities = 35%; w/ t(6;9) = 50%; w/ 5q loss = 27% monosomy

First Author, Year, setting	Study design	Period	Age at diagnosis	Number of cases	Early death		Survival or hazard of death
							7 = 32%
11. Walter RB, 2011, US[226]	Clinical trials	SWOG: 1986–09 MDA : 1995–08	SWOG: 17–88 MDA: 14–89	SWOG: 1,127 (non-APL) MDA : 2,238 (non-APL)	Death within 28 days of initiation of therapy	SWOG: 11.1% MDA : 9.9%	Not described
12. Bradley CJ, 2011, US[228]	Population-based	1999–2006	21–64	523	N/A	N/A	HR for black vs. white patients = 1.43 HR of uninsured and publicly vs. privately insured patients = 1.29 and 1.39
13. Pulte D, 2012, US (SEER)[229]	Population-based	1992–1996 2002–2006	≥ 15	N/A	N/A	N/A	5-y RS for acute leukaemias, 1992–96 and 2002–06, respectively: 15–64y = 28% and 39% (nHw), 26% and 27% (b) and 29% and 38% (H); ≥ 64 = 5% and 6,5% (nHw), 5% and 7% (b) and 7% and 11% (H)*
14. Rubnitz JE, 2012, US (St. Jude)[227]	Clinical trials	AML91: 1991–96 AML97: 1997–02 AML02: 2002–08	≤ 21	351	N/A	N/A	3-y OS AML91/97 and AML02 protocols, respectively: 0–9 y = 60% and 75%, 10–21y = 48% and 69%. TRM was higher for patients aged 10–21y
15. Juliusson G, 2012, US (SEER) and Sweden[236]	Population-based	1997–2006	0–84	<30y: 65 30–44y: 171	N/A	N/A	5-y OS for AML unselected patients aged <30y and 30–44y, respectively = 60% and 49%
16. Borate UM, 2015, US[231]	Population-based	2007–2011	19–64	5,541	N/A	N/A	Median OS = 16mo, worse for uninsured or Medicaid, single or divorced, and lower county-level income patients

Abbreviations: ALL, acute lymphoblastic leukaemia; APL, acute promyelocytic leukaemia; AML, acute myeloid leukaemia; b, black; BFM, Berlin-Frankfurt-Münster; DS, Down syndrome; EFS, event-free survival; HR, hazard ratio; MDA, MD Anderson Cancer Center; MRC, Medical Research Council; mo, months; MDS, myelodysplastic syndrome; N/A, not applicable; nHw, non-Hispanic white; OS, overall survival; RS, relative survival; SEER, Surveillance Epidemiology and End Results; TRM, treatment-related mortality; UK, United Kingdom; US, United States; NALL (non ALL); St. Jude, St. Jude Children's Research Hospital; SWOG, Southwest Oncology Group; y, years; w, white. *Survival for Hispanic may be over-estimated because of the lack of specific life tables for this group.

Chapter 4: Materials and Methods

This chapter is divided in four sections. In the first section (study design), I give an overview of the main data used in survival analysis with their pros and cons. In the second section, I specify the source of data and variables I have used. In the third section, I explain the methods I have deployed in my studies. In the fourth section, I describe the main biases that can occur when using population-based studies.

4.1 Study design

Survival can be estimated using data from population-based or hospital-based cancer registries. The studies in this thesis are all population-based cohort studies.

The main characteristics, advantages and pitfalls of both registries data are summarised in Table 4.1. Hospital-based registries can provide detailed data on individual patient such as diagnostic methods, treatment protocol, and level of abandonment of treatment. These are very useful for the estimation of survival of patients according to treatment protocols, stage of disease, risk stratification, among others. However, these data may not be representative of the entire population and may provide inaccurate demographic data. Population-based studies are therefore important for assessing the burden of cancer in the general population, providing more accurate estimates of incidence, mortality and survival. These measures allow for epidemiological research that investigates the aetiology of the disease (e.g., cancer) and the effect of preventive and therapeutic strategies, as well as guidance of health-care planning.

Table 4.1: Main differences between hospital-based and population-based cancer registries. Adapted from Valsecchi and Steliarova-Foucher, *Lancet Oncol* 2008[242]

	Hospital-based cancer registry	Population-based cancer registry
Aims	To provide data for: - hospital's cancer programme - individual patient - hospital administration	To provide data on general population for: - assessment of cancer burden - assessment of preventive measures - health-care planning - patient-care assessment - causal research
Background population	Proportion of population living in referral area	General population, defined by residence area and enumerated in population census
Data sources	- Hospital departments - Autopsy reports (in same hospital) - Outpatient records	- Hospital departments - Autopsy reports - Outpatient clinics - Death certificates - General practitioners - Screening programmes - Health insurance companies - Population registries - Hospices
Registration sources	On-site search	- Notification - Active search in referral hospitals - Linkage with other data sources
Output	- Frequencies of cancer types - Statistics on treatment abandonment - Survival of patients, according to stage, treatment protocols, and other criteria	- Incidence - Mortality (if full access to regional or national data) - Prevalence - Population-based survival
Pitfalls		- Incidence of cancer in general population cannot be derived, - Imprecise demographical data, - Incomplete long-term follow-up data, - Patients characteristics and survival not necessarily representative of patient population - Erroneous diagnostic data - Missing or incomplete information on treatment - Missing or incomplete follow-up for late effects of treatment (apart from multiple cancers)

Hospital based data can be used for observational studies or interventional studies (clinical trials). Clinical trials are essential to evaluate the effect of cancer treatment on a selected population. They are recognised as the "gold standard" practice in the unprecedented success of increasing childhood leukaemia survival, as well as other types of cancer. However,

these studies are subject to selection bias because they reflect the experience of those patients who were able to get to the hospital and be admitted, but they are not representative of the entire population. Moreover, clinical trials usually exclude patients with advanced disease or comorbidities. Clinical trials determine the *efficacy* of treatment in a selected group of cancer patients, whereas population-based studies provide information on the *effectiveness* of cancer services in unselected populations.[243]

4.2 Data source

4.2.1 The California population and health system

According to the US Census Bureau (http://www.census.gov), in July 2015 the estimated population of California was 39,144,818. Currently, the proportion of Hispanics has slightly surpassed the white, non-Hispanic proportion (Figure 4.1). In California, the health systems differ according to age as described below.

Health Systems in California

The California Children's Services

The California Children's Services (CCS, www.dhcs.ca.gov/services/ccs) is a statewide program operated by the State Department of Health Care, which provides treatment for children and adolescents with certain conditions such as cancer, congenital heart disease and physical disabilities, among others. Eligibility criteria include age less than 21 years, being resident in California, a family income of less than USD 40,000 and a medical condition covered by the CCS. Under these criteria, all children and adolescents with cancer in

California are entitled to state coverage of the costs of treatment, regardless of their family's ability to pay. The majority of children's hospitals in California that treat patients with cancer are also specialised cancer centres (see Chapter 5).

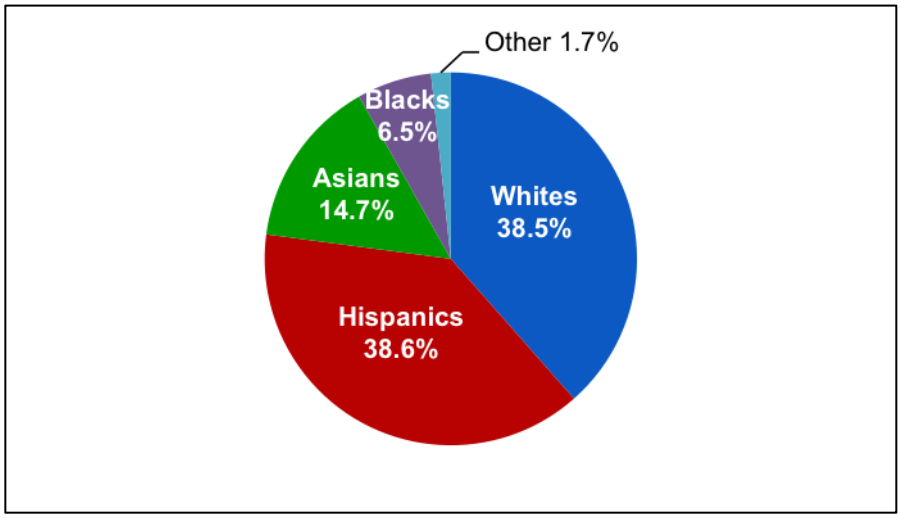

Figure 4.1: California population by race/ethnicity. Adapted from the US Census Bureau, 2014 (www.census.gov).

California's Medicaid program

Unemployed patients and those with low resources who are aged 21 years or older are eligible to apply for the California's Medicaid program (also called Medi-Cal) and to receive coverage for cancer and most other conditions. Patients aged 65 years or older are entitled to Medicare coverage, and they may also be eligible for supplemental insurance through Medi-Cal ("dual eligibility"). The Medicare and Medicaid are different programs established by the United States federal government in the mid-1960s. While Medicare' rules are the same all over the country, Medicaid programs in each State have different rules and allowances.

One recent study[244] estimated that 7%–10% of Medi-Cal expenditure is spent on cancer care. The authors used California Cancer Registry data, and found wide disparities in survival, quality of care and stage of cancer diagnosis in relation to health insurance coverage. Overall, Medi-Cal, dual eligible Medicare-Medi-Cal or uninsured patients had cancer diagnosed at a more advanced stages, with worse prognosis, and poorer quality of care than those with private insurance, Medicare alone or other types of government coverage (such as military and government employees). These disparities varied by type of cancer examined.

*The Patient Protection and Affordable Care Act (*ACA or *"Obamacare")*

Several studies have shown that cancer survival is worse among young adults without health insurance. For instance, Aizer et al[245] used SEER data to examine the association between health insurance status and outcomes among patients aged 20–40 years with specific types of cancer. Patients with health insurance were more likely to have received definitive cancer therapy, less likely to have metastatic disease at initial presentation, and had lower all-cause mortality than uninsured patients. Another study[246] revealed that, compared to young adults without cancer history, cancer survivors, particularly those aged 20–39 years, may forgo cancer treatment due to high medical costs.

The Patient Protection and Affordable Care Act (ACA or "Obamacare") is a US federal statute signed into law by President Barack Obama on 23 March 2010 that aims to expand insurance coverage for many uninsured patients, including young adults (http://www.dpc.senate.gov/healthreformbill).

This program allows patients up to 26 years to remain on their parents' health insurance plan, prevents insurance companies from refusing coverage for patients with pre-existing conditions and expands Medicaid coverage, among other measures.

4.2.2 The Surveillance, Epidemiology and End Results (SEER) Program and the California Cancer Registry (CCR)

For this thesis, I used data from the California Cancer Registry (CCR), which participates in the Surveillance Epidemiology and End Results (SEER) Program (http://seer.cancer.gov/about/overview.html) of the National Cancer Institute (NCI). SEER is a coordinated system of population-based cancer registries across the United States, which has been collecting and publishing cancer incidence and survival data since 1973. Initially covering 9 geographic areas in the US, SEER has grown to cover 18 areas, corresponding to approximately 30% of the US population, based on the 2013 population.

The racial/ethnic proportion of population covered by SEER corresponds to approximately to 25% of whites, 26% of African Americans, 38% of Hispanics, 44% of American Indians and Alaska Natives, 50% of Asians, and 67% of Hawaiian/Pacific Islanders (http://seer.cancer.gov/registries/data.html).

SEER collects data on patient demographics (including age, sex and race/ethnicity) and tumour information (primary tumour site, morphology, stage at diagnosis, first course of treatment, and follow-up for vital status). Some variables are derived, such as subsequent tumour, which is based on the fact that the same patient has another tumour in the database with a

higher sequence number. The characteristics of the SEER population are very close to those of the total US population in terms of poverty level and education. SEER registries tend to have more foreign-born inhabitants and urban areas than the rest of the United States. The population information used for cancer rates estimation is regularly obtained from the Census Bureau Statistics (http://www.census.gov) and the mortality data reported by SEER are extracted by the National Centre for Health Statistics (http://www.cdc.gov/nchs/).

The CCR was established in 1985 and is recognized as one of the leading cancer registries in the world. Cancer reporting became a statutory requirement in California in 1988. To date, the CCR has collected detailed information on more than 3.4 million cases of cancer diagnosed from January 1988 onwards, and an estimated 162,000 new cases of cancer are reported annually.[247] The CCR standard for completeness of ascertainment, estimated using time series methods, is at least 98%. All data reported by CCR are extracted by trained tumour registrars, directly from the medical records of each patient. Table 4.2 shows the history of cancer registration in California.

Follow-up information in CCR

The CCR, as well as other SEER registries, routinely conducts exhaustive active and passive follow-up activities in order to capture the date of last known vital status, which is available for all cases. Active follow-up includes contact with the patients, their relatives and/or physicians. The passive follow-up is done via linkage to other data sources, including the following: State Vital Statistics, National Death Index (NDI), Social Security Administration,

Office of Statewide Health Planning and Development (OSHPD, hospital discharge data), centres for Medicare and Medicaid Services (CMS), State birth certificates, State motor vehicles, State voter registration, religious groups, labour unions, welfare agencies, pathology and doctors records, and hospital cancer registries information. In the CCR, the majority of patients have full dates of last follow-up (day, month and year). There may be a small number of missing day and/or month of last known vital status as discussed later in this chapter in section 4.3.4. The year of last vital status is never missing in the CCR.

Current follow-up information in the CCR is defined as “contact with the patient within 15 months of the date of last reported follow-up”. Each registry in California should report the date of last contact and known vital status within 18–22 months of SEER annual data submission. Even though current follow-up is preferred, any information should be submitted, whether current or not.[248] The calculation of follow-up percentage done by SEER/CCR is provided in Appendix 2.

Survival analyses conducted by SEER/CCR are based on the reported date of death or on the documented date of last contact when the patient is alive (“reported alive” method). This method has been considered more accurate than the “presumed alive” method used by the National Program for Cancer Registries (NPCR).[249] The NPCR uses passive follow-up to ascertain the last vital status and if dead, the date of death, through linkage with the National Death Index. Therefore, if an individual is not reported to be dead in the National Death Index, she/he is assumed to be alive. A recent study conducted by Pinheiro et al.,[249] compared survival estimates for certain types

of cancer and by race/ethnicity using the “reported alive“ (SEER) and “presumed alive” (NPCR) methods. The authors found that, compared to the “reported alive”, the “presumed alive” method overestimated survival by 0.9%–6.2% depending on the type of cancer and race/ethnic group (higher survival overestimation among Hispanics).

Because all the registries in the CCR also participate in SEER, they are bound by the SEER data quality standards. The SEER minimal acceptable standard for follow-up is 80% for children and 90% for adults, although the contractual standards are ≥ 90% and ≥ 95% respectively.[250]

Loss to follow-up may be more significant for young patients (20 years or younger) because they often move (e.g., to attend college) and tend to have less contact with sources that would generate passive follow-up vital status for the cancer registry (social security, Medicaid and hospital admissions). Unless they experience disease relapse, young people tend not to go to hospitals. In addition, in the United States, when children grow up to the age of 26 years or older (the age limit has been expanded since implementation of the ACA), they are no longer under their parents’ health insurance plan, and may have a new doctor, be treated at a new hospital and even neglect to tell their new physician about a previous cancer diagnosis. Therefore, a supplementary source of information may be lost.

Immigrants such as Hispanics and Asians are more likely to have incomplete follow-up than whites and blacks.[249] Immigrants who are severely sick may return to their countries due to financial burden and/or to be close to their relatives. The deaths of these patients would then not be captured in the National Death Index US statistics. However, as discussed in a previous

study, it is unlikely that the small number of Hispanics patients who migrate-out of the US would bias survival estimates significantly.[251] California annual interstate migration is about 1.2%, considered the lowest in the US.[252]

Table 4.2: History of cancer registration in California. Adapted from the California Cancer Registry at https://www.cdph.ca.gov/programs/ccr/Pages/AboutUs.aspx.

Year	Landmark
1947	California Tumour Registry established in selected large hospitals
1960	Alameda County Cancer Registry established as the first population-based cancer registry in California
1969	San Francisco – Oakland Registry included in NCI Third National Cancer Survey
1972	Cancer Surveillance Program of Los Angeles County established
1973	San Francisco – Oakland Registry included in NCI's SEER Program
1983	Cancer Surveillance Program of Orange County established
1985	California Cancer Reporting Law signed into effect (CCR established)
1988	Population-based cancer reporting initiated statewide
1992	Cancer Surveillance Program of Los Angeles County included in SEER Program San Jose-Monterey Registry included in SEER Program
1997	Fifty years of cancer reporting in California
2000	Published ten years of complete statewide cancer reporting
2001	Greater California Registry included in SEER Program
2007	Twenty years of statewide population-based cancer reporting
2009	Published 20 years of complete statewide cancer reporting

The California Cancer Registry works in collaboration with 10 cancer registries regions, which are described below:

Regions 1 & 8: Cancer Prevention Institute of California (Region 1 covers Santa Clara Region and Region 8 covers the Bay Area Region)

Region 2: Cancer Registry of Central California

Region 3: Sacramento and Sierra Cancer Registry

Region 4: Central Coast Cancer Registry

Region 5: Desert Sierra Cancer Surveillance Program

Region 6: Cancer Registry of Northern California

Region 7: Cancer Registry for San Diego and Imperial Counties

Region 9: Cancer Surveillance Programme (Los Angeles county)

Region 10: Orange County Cancer Registry.

4.2.3 Variables available in the California Cancer Registry

The California Cancer Registry makes several variables available to researchers that are not, or have only recently become, available in the SEER public use data. These include information on health insurance status, systemic treatment (chemotherapy, hormone therapy), facility that first report the cancer, and an index of socioeconomic status based on census block group of residence at time of cancer diagnosis. Most of variables used in this thesis have been available in the California Cancer Registry from 1988 onwards. Health insurance has been routinely collected since 1996 and haematopoietic stem cell transplantation since 2003, although in some cases this information is available before this year. These variables are specified below, based on the California Cancer Registry Data Dictionary.[253]

Patient's sociodemographic variables

Age at diagnosis: Age, in complete years, when the patient was first diagnosed with this tumour. In the study of acute lymphoblastic leukaemia, age was categorized in 5 groups: <1, 1–4, 5–9, 10–14 and 15–19 years because the survival of infant with this disease is significantly worse than that of older children. In the acute myeloid leukaemia studies, the age groups I used were: 0–9, 10–19, 20–29, 30–39 years. Young adults (20–39 years) were included because acute myeloid leukaemia is essentially a disease of

older patients and this age group has a worse prognosis than younger patients with acute myeloid leukaemia.

Sex: Sex of the patient was categorised as male or female.

Patient identification: It is a unique statewide identification number assigned by the California Cancer Registry to identify each registered patient. It is a numeric code. This code is also used to identify patients with more than one primary tumour and allows for identification of all tumours for a given patient

Date of birth: day, month and year of birth.

Race/ethnicity: SEER race codes reflect the values the cancer registries report to it, which are usually obtained from medical records. For California Cancer Registry, race is obtained from various sources, including medical records, which can be based on self-reported data. Self-reported information takes priority over other documentation in medical records and is considered the "gold-standard" for race classification.[254] According to the California Cancer Reporting System Standards Volume I,[248] when the patient's race is reported differently by two or more sources within the medical record, race should be coded using the following sources in the succeeding priority order: 1) the patient's self-declared identification, 2) documentation in the medical record, 3) dictated reports, 4) nurses' notes, and 5) death certificate.

Ethnicity is not a collected information, but derived from other variables based on the North American Association of Central Cancer Registries

(NAACCR) algorithms. The NAACCR Hispanic Identification Algorithm (NHIA) algorithm is used to identify Hispanic ethnicity and the NAACCR Asian Pacific Islander Identification Algorithm (NAPIIA) to identify more specific Asian subgroups (http://www.naaccr.org/). Both algorithms are described in the Appendix 3.

In the California Cancer Registry, race/ethnicity is categorised in the following groups: non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, non-Hispanic American Indian, and other/unknown. Hispanic ethnicity is recorded independently of race; therefore, Hispanic people may be of any race. It has been shown that the majority of people of Hispanic ethnicity are of white race.[254]

Health insurance status (available from 1996 onwards): Health insurance status at time of initial treatment began to be routinely collected by the California Cancer Registry in 1996, therefore in all of my studies, this variable will be analysed from 1996–2011. Heath insurance has been divided in 4 categories as follow: 1) Private insurance, which includes health maintenance organizations, preferred provider organisations, managed care, and fee-for service, 2) Public insurance includes Medicaid, Medicare, military*, Veterans Affairs, Indian/Public Health Service and county funded, and other government-assisted programs, 3) Uninsured refers to patients with no insurance, self-pay, and 4) Insurance unknown or not otherwise specified.

*Some researchers considered military under private insurance. In this dissertation, it was included under public insurance and accounted for <=1% of cases.

Neighbourhood socioeconomic status (SES) has been available in the registry from 1988 onwards. Individual information on SES is not routinely collected by population-based cancer registries. The California Cancer Registry uses an aggregate-level SES index as a surrogate measure at the census block group level. This index was created by Yost et al.[255] in 2001 and has been successfully used by the California Cancer Registry in epidemiological studies of incidence[256] and survival.[257] Census block groups contain approximately 1,000 individuals and are considered relatively homogenous regarding SES factors. There are three criteria for census block groups. The first criterion involves a total population larger than zero, excluding census block groups without patients; therefore all census block groups are included in the analysis. The second criterion is median income greater than zero, excluding non-residential areas such as penitentiaries and dormitories. Finally, the third criterion implicates population aged 25 years or older bigger than zero, because this is the group of individuals included in the education index.

In 1990, there were 21,519 census block groups in California, and this number has increased to 23,212 in 2010 census.[255, 258] The neighbourhood SES variable combines seven indicator variables into one single measure using a principal component analysis. These indicators are surrogate for occupation, poverty, income and education. The occupation variables are the proportion of individuals with a blue-collar job and proportion of people older than 16 years in the workforce without a job. The poverty measure refers to the proportion below 200% of the poverty level. The education index was developed by Liu et al.,[259] and takes into account the proportion of people in a

census block group with certain level of education and the number of years taken to obtain that level of education. The income indicators are median household income, median home value, and median house rent. The correlation of each of the seven indicators with the neighbourhood SES is described as follows: education index = 0.87, proportion with a blue-collar job = –0.70, proportion of individuals aged 16 years or older without a job = –0.68, median household income = 0.85, proportion of the poverty level = –0.87, median house rent = 0.63, and median house value = 0.78. Each block group received a score and then all the block group level SES scores were divided into quintiles based on the statewide distribution. Each patient was assigned a neighbourhood SES level based on the census block level he/she lived at the time of leukaemia diagnosis.

Tumour variables

Tumour behaviour: This variable corresponds to the fifth digit of the ICD-O-2 or ICD-O-3 morphology code that indicates the malignancy or behaviour of this tumour. Only tumours with fifth digit equal “3” (malignant/invasive) were included in my studies.

Tumour identification: It is unique statewide identification number assigned by the California Cancer Registry to identify each tumour. It is a numeric code. This variable with the **patient identification** allows for the identification of patients with more than one primary tumour.

Date of diagnosis: day, month and year of leukaemia diagnosis

ICD-O-3 Morphology code: The first four digits of the ICD-O-3 morphology code, indicates the histology/cell type of this tumour. Coded directly for cases diagnosed 2001 and forward. Cases coded prior to 2001 were converted to ICD-O-3.

Immunophenotype: For acute lymphoblastic leukaemia, immunophenotype was derived from the ICD-O-3 morphology codes and subdivided in B-cell, T-cell or NOS acute lymphoblastic leukaemia.

Sequence number: The California Cancer Registry provides a variable that indicates the sequence of all reportable neoplasms during the patient's lifetime as determined by the central registry. When two or more tumours are diagnosed simultaneously, the tumour with the worse prognosis is assigned the lowest sequence number. In this thesis, I used the first, primary malignancy of each patient. For the acute lymphoblastic leukaemia study, I have also examined subsequent (secondary) tumour.

Diagnostic confirmation: Indicates whether, at any time during the patient's medical history, there was microscopic confirmation of this cancer. In my studies, microscopic confirmation was 99.8% for acute lymphoblastic leukaemia, 99.9% for acute promyelocytic leukaemia and 99.5% for non-APL acute myeloid leukaemia

Treatment variables

Chemotherapy: Identifies the type of chemotherapy given as first course of treatment at any facility. If chemotherapy was not given, codes are provided to record that reason, e.g. chemotherapy was contraindicated, recommended but not given, refused, or the patient died before start of treatment. In my studies, this covariate was treated as a binary variable: chemotherapy “yes” (Y) or “no” (N). There is no information on the type of drugs, dosage or length of treatment.

Radiotherapy: This covariate identifies the modality of radiation therapy given as first course of treatment. It was used in the acute lymphoblastic leukaemia study as binary: radiotherapy performed Y or N.

Haematopoietic stem cell transplantation: This variable has been routinely collected for cases diagnosed from 2003 onwards, but has also been reported for many patients diagnosed during 1996–2002 and it was used in this thesis in the study of acute myeloid leukaemia (Chapter7).

Treatment facilities *(HOSPNO):* The California Cancer Registry records the hospital or other facility with the earliest admission date for each tumour. I further classified these hospitals as children hospital Y/N (acute lymphoblastic leukaemia study) and hospital affiliated with NCI-designated cancer centres, Y/N (acute myeloid leukaemia studies).

Follow-up variables

Date of last known vital status: date of last known vital status available for the patient, or date of death if patient deceased.

Vital Status: patient's vital status as of the date of last contact categorised as "dead or "alive".

Cause of death: The underlying cause of death is coded by the National Centre for Health Statistics and the California Department of Public Health based on causes of death reported in the death certificate.

4.3 Methods

4.3.1 Introduction to survival analysis and early death

4.3.1.1 Survival

In this thesis, I use the term cancer survival to mean the probability that a patient is still alive at a given time since cancer diagnosis. The event of interest (failure) is *death* and the survival time is measured from the date of cancer diagnosis (*time origin*) until death (*end-point*). Figure 4.2 shows the survival time since clinical diagnosis. The survival time can be recorded in days, weeks, months or years, whichever is more appropriate to the study design and subject matter. For my studies in this thesis, I used survival time in years.

Some types of cancer, such as breast or colorectal cancer may be diagnosed by screening, before the symptoms occur. This situation may cause the "lead time bias", which means that survival time increases, but the

death date remains the same, therefore, there is not real survival improvement. For acute leukaemias, diagnosis is usually made after symptoms presentation.

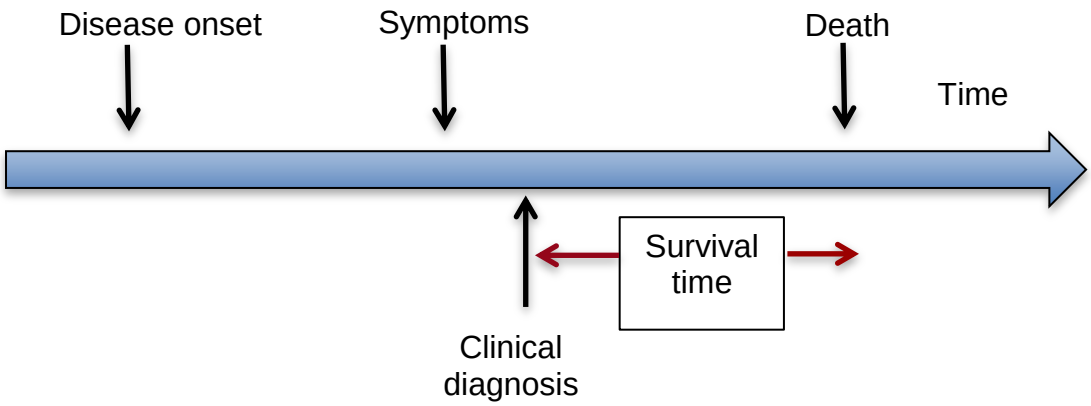

Figure 4.2: The natural history of cancer and estimation of survival time for a patient diagnosed clinically. Adapted from Dickman et al., *J Intern Med* 2006[260]

A frequent feature in the analysis of survival data is censoring, which occurs when the event of interest (death) is not observed during the course of entire follow-up, leading to an incomplete observation of the survival time. The reason for censoring is that, in general, it is not possible to follow up all cancer patients until death. Some patients will emigrate, some will experience a "competing" event and others will not experience the event before the end of the study. It is important to incorporate information on censoring into the analysis of survival data.

Survival is described using two terms: the survival function and the hazard function. The survival function $S(t)$ gives the probability of surviving beyond some specific time t: $S(t) = \Pr(T > t)$, where T, a random variable, is the survival time $(T \geq 0)$ and t is the specific value for T. Therefore, $S(t)$ is the

probability of a patient still being alive (have not had the event) at time (*t*), and varies from 0 to 1. A survival curve plots the survival function over time (*t*).

The hazard function *h(t)* or hazard rate gives the instantaneous hazard at time *t* for the failure event (death) to occur provided that the individual has survived up to just before time *t*.[261] The range for the hazard varies from 0 to infinity and depends on the measure of time used (days, weeks, months, years, etc.). The hazard function is advantageous in survival analysis because it considers the immediate risk attached to a patient known to be alive at time *t* and has proved to be particularly useful in comparing the survival of different groups of individuals. While the survival curve can only stay the same (e.g. nobody dies during a study to test a new drug) or decrease over time (patients die over time), the hazard can oscillate up and down over time.

For the analysis of survival data, special methods are required because survival time is never negative and survival times are often *censored*. A major assumption in most survival analyses, including those used in this thesis, is that censoring is non-informative, i.e., time to death from cancer is independent of time to censoring (alive or death due to other causes). This means that the patients who have not been censored by a given time are a random sample of the patients still at risk. Non-informative censoring does not introduce bias to survival estimation, whereas informative censoring does. In my studies, it is reasonable to assume that informative censoring was not a concern due to two main reasons: firstly, because there was not a large amount of loss to follow-up, and secondly, there are not significant competing causes of death among the young population studied. In addition, I have also provided a descriptive analysis of the causes of death in each study, and my

findings showed that > 90% of deaths occurred due to acute leukaemia. Some other causes reported in death certificates (e.g., infection and haemorrhage), may also be caused by leukaemia.

4.3.1.2 Early death

Because of the severity of acute myeloid leukaemia, this malignancy requires initiation of treatment as soon as possible. This is specifically relevant for acute promyelocytic leukaemia, a subtype of acute myeloid leukaemia, because the patients often present bleeding, thrombosis and/or severe infection in the first days and weeks after diagnosis. Thus, treatment with chemotherapy and ATRA should be initiated as soon the disease is suspected. Failure to do so can lead to early death.

In this thesis, in addition to survival, I examined early death as an event of interest in acute promyelocytic and acute myeloid leukaemias studies (Chapters 6 and 7). In my studies, early death was defined as death within 30 days of leukaemia diagnosis, and was estimated as the proportion of individuals who died in this period. This definition varies slightly according to different studies (Supplementary Table in Chapter 6). In addition to 30-day mortality, I have also investigated 7-day mortality for patients with acute promyelocytic leukaemia because they have a greater risk of death in the first days after diagnosis. The Pearson's chi-squared test (χ^2) was used to test the null-hypothesis that the frequency distribution of early death was equal within strata for each covariate.

4.3.2 Estimation of cancer survival

A variety of methods can be used to estimate survival. The main methods are summarised in Table 4.3. Cause-specific survival estimates the probability of dying due to a given disease, e.g. cancer. In this case, the event of interest is death due to cancer. Cause-specific survival is not often used in population-based studies because a reliable and accurate cause of death is not usually available in cancer registries, especially in poor-resource countries.[262]

Most often, the estimation of cancer survival in children, adolescents and young adults (< 45 years) is performed using overall survival because, at least in the developed countries, the competing causes of death are rare. The event of interest is *all* deaths and it does not take into account the cause of death. When we have individual data, overall survival can be estimated using the Kaplan-Meier (or product limit) method, which I have used in this thesis.[263]

Table 4.3: Measures of cancer survival. Adapted from Dickman and Hakulinen, 2006[260]

	Advantages	Issues
Observed, overall, absolute or crude survival	Reflects total mortality. May be more relevant to the patient and/or clinician	Comparisons may be confounded by age
Cause-specific survival	Reflects mortality due to cancer	Requires certification of coding the underlying cause of death
Relative / net survival	Reflects mortality due to cancer, capturing both direct and indirect mortality	Requires estimates of expected survival of the cancer patients, which is derived from mortality in the general population ("background" mortality)

The Kaplan-Meier method

The Kaplan-Meier method is a non-parametric or "distribution-free" estimate of the survival function, which allows us to estimate survival probabilities in the presence of censoring. A major assumption of the Kaplan-Meier method is

that censoring is non-informative, as described in section 4.3.1.1. In the Kaplan-Meier method, the follow-up time period is divided into intervals so that each interval contains one survival time *t*. Each death starts one interval, which ends just before another death occurs. We estimate the probability of occurrence of death at each death time, which is calculated as the number of deaths at that time divided by the number of individuals at risk at that time (i.e. not dead and not censored).[264] We then subtract these probabilities from one. These new consecutive probabilities are multiplied cumulatively across all failure times to obtain the estimated survival probabilities. The estimated survival probabilities are constant between consecutive survival times and decrease at each death time, leading to the characteristic “stair step” Kaplan-Meier survival curves. This is illustrated in Figure 4.3, which used a sample of data from one of my studies presented later in the thesis. The Kaplan-Meier survival curves can be estimated separately for different groups of individuals.

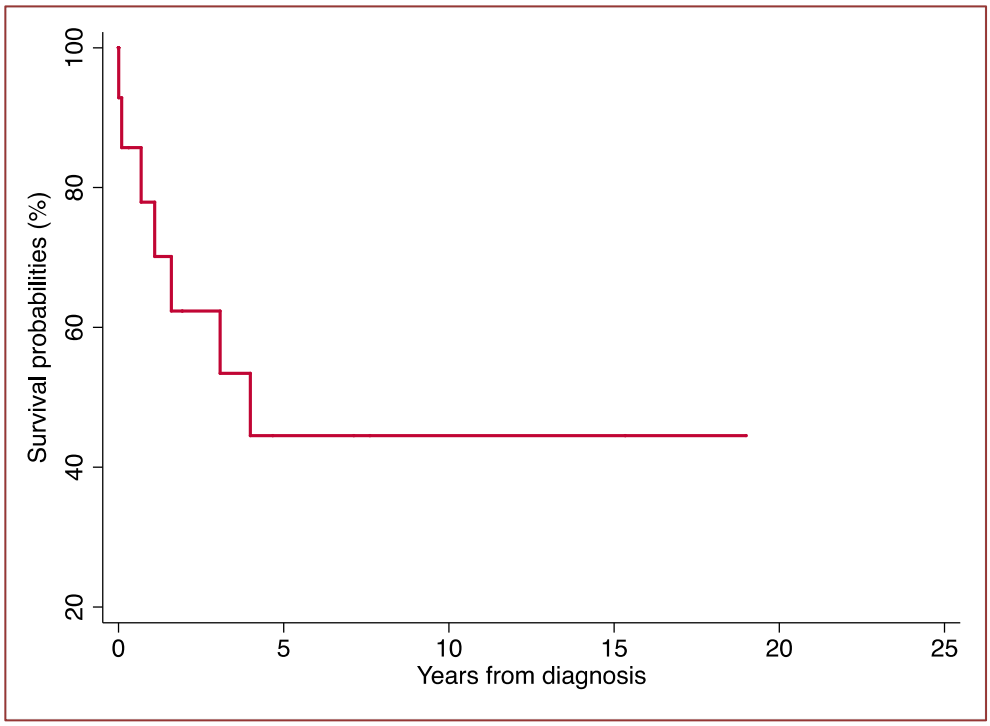

Figure 4.3: The characteristic "stair step" Kaplan-Meier survival curve

The main reasons to use nonparametric methods such as Kaplan-Meier include their relative simplicity, the fact that survival data can be nicely displayed in graphs, including when there is censoring, and the possibility to easily compare patterns of survival among two or more groups of patients. Additionally, this method can be used to inform more complex modelling of survival data.

The log-rank test is a non-parametric test that can be used to compare the survival curves of two or more groups of individuals across various time points. When a large enough sample is used, the log-rank test is a valid and powerful test of hypothesis that the survive curves (S) of two or more groups are different:[265]

Null hypothesis: S1(t) = S2(t) for all times *t*

Alternative hypothesis: S1(t) ≠ S2(t) at any time *t*

The log-rank test gives a *P*-value for the hypothesis test, which represents the strength of the evidence against the null hypothesis of no difference between one or more groups. The smaller the *P*-value, the stronger the evidence against the null hypothesis. However, the log-rank test does not provide an overall measure of the association between survival and the explanatory variables. Therefore, it does not estimate the magnitude of the difference in survival for different groups of individuals being compared.

The cohort and period approaches

In the acute lymphoblastic leukaemia study, 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 classical cohort-based approach because most patients had been followed for at least 5 or 10 years, respectively, during these time periods. The traditional cohort-based approach provides survival estimates using all the observed follow-up data. There was not follow-up information to estimate 10-year survival for patients diagnosed during calendar period 2004–2011 using this approach.

For the acute promyelocytic and non-APL acute myeloid leukaemia studies, I chose to use the period approach[266] for the calendar period 2004–2011 when patients had less than 5 (or 10) years of follow-up. The period approach provides a short-term prediction of their survival up to 5 (or 10) years after diagnosis on the assumption that their probabilities of survival will be the same as those observed during the most recent years for which follow-up data were available. The period approach deploys exactly the same data on patients and their follow-up as are deployed in the cohort-based

approaches; it just combines the probabilities vertically (calendar period) instead of horizontally (year or period of diagnosis) (Figure 4.4).[267] Estimates of long-term survival using the period approach are usually higher than the long-term survival estimated by cohort-based analysis given improvement in survival over time. The estimates from the cohort-based and period approaches will be the same when there is no change in the disease outcome over time.

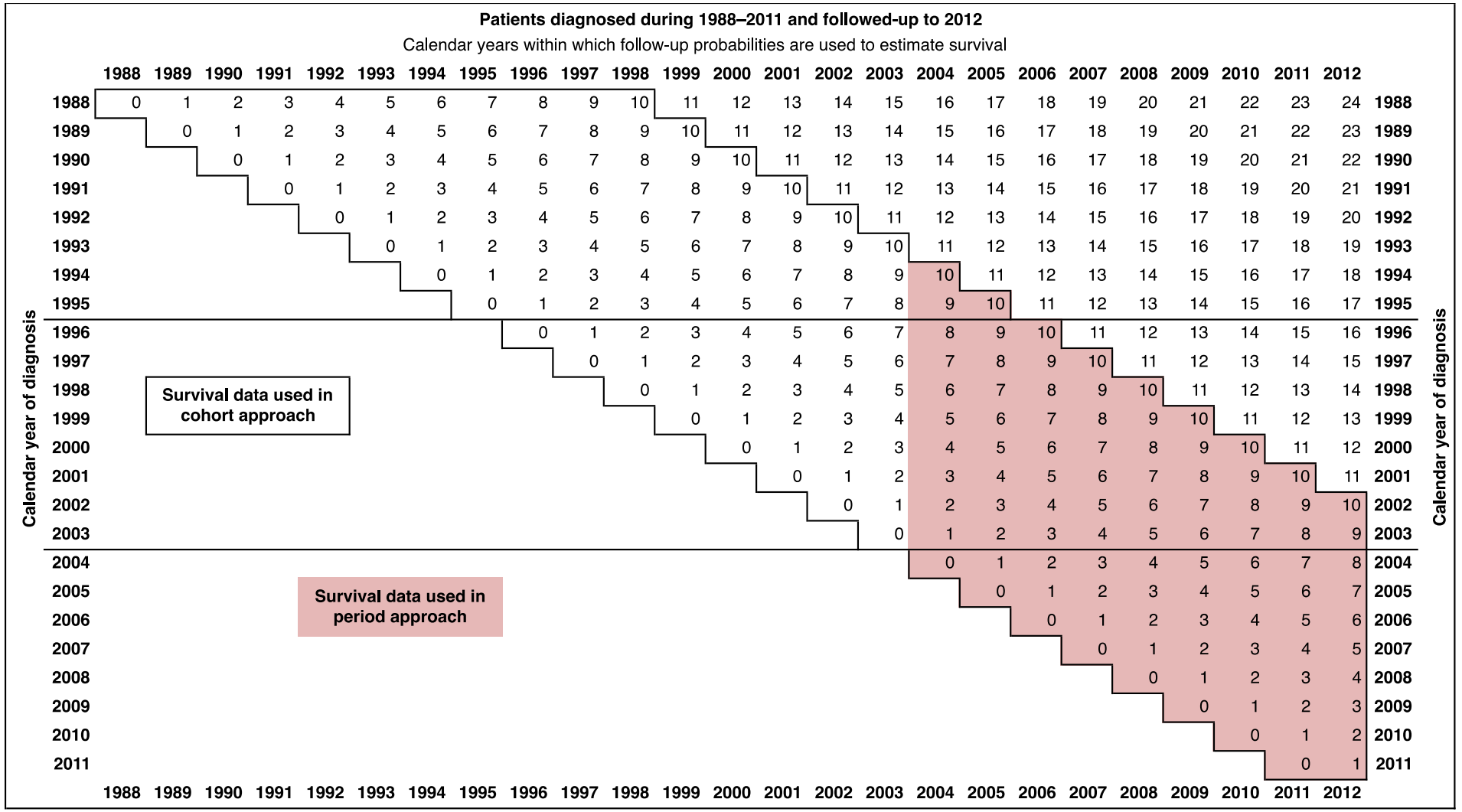

Figure 4.4 Data used for period and cohort approaches. The pink frame shows the data used to estimate 10-year survival for the 2004–2011 period using the period approach. The traditional cohort approach was used to estimate 10-year survival during 1988–1995 and 1996–2003 (white frame) and 5-year survival in all calendar periods. The numbers within the cells represent the years of follow-up since acute leukaemia diagnosis.

4.3.3 Measuring association: Cox models and logistic regression

Although one may be interested in the distribution of survival time in one particular population, often researchers and clinicians are interested in comparing survival distributions between two or more groups of people. In addition, when explanatory variables are available, their influence on survival (or another event such as early death) is often assessed. This can simply be done by looking at Kaplan-Meier plots within groups or, in the case of early death, by tabular comparisons between death/no death and the exposure variable. In my three studies, I aimed at investigating the association between survival and early death, and sociodemographic and selected clinical factors. I used univariable and multivariable models as described below.

The Cox proportional hazards model: hazard ratios for death

In order to measure the association between survival and the explanatory variables, I used the Cox proportional hazards model, the most frequently used model in survival analysis, developed by David Cox in 1972.[268] The Cox model allows for the estimation of the magnitude of an association between survival and each explanatory variable (univariable analysis) and can also account for multiple independent variables simultaneously (multivariable analysis).

An important feature of the Cox model is that it assumes that the individual and the baseline hazard rates may vary over time, but their ratio, called the hazard ratio, is assumed to be constant at all times *t* across groups. This assumption is known as the proportional hazards assumption, characteristic of this model. This model also accounts for censoring.

Formulation of the Cox model

Under the Cox proportional hazards model, the hazard function at time *t* for individual with values x1, x2..., x_k for the explanatory variables X1, X2... X_k is formulated as:

$$h(t|x_{1,}\, x_{2...,}\, x_k) = h_0(t) \exp(\beta_1 X_1 + \beta_2 X_2 .... + \beta_k X_k)$$

where $h_0(t)$ is the baseline hazard and $\beta_{1,2,K}$ are the regression coefficients to be estimated from the model; these are the log hazard ratios.

A hazard ratio equal to 1 reveals no association between the hazard of death and the explanatory variable. A hazard ratio different than 1 indicates that there is an association between the hazard of death and the explanatory variable. We incorporate sampling error into these estimates using a confidence interval (CI) and a *P*-value test. The CI gives a range of plausible values for the true hazard ratio. I used 95% CIs, meaning that there is a 95% chance that the true population hazard ratio is included in this interval. If the confidence interval contains 1, it means that there is no evidence for a statistically significant difference between the groups of individuals being compared in a test of the null hypothesis at the 5% level.

The P-value for the hypothesis test demonstrates the strength of the evidence against the null hypothesis. Two statistical tests are commonly used to test the null hypothesis: the Wald statistic and the likelihood ratio test.

Testing the proportional hazards assumption

To test the proportional-hazards assumption in my three studies, I examined the log-log survival plots and used the Schoenfeld residuals[269] to confirm the results.

If an explanatory variable satisfies the proportional-hazard assumption, the graph of the log-log survival function versus the survival times in two or more groups should be approximately parallel. If the proportional-hazard assumption is not met, the curves will not be parallel and can even cross each other.[270] However, this approach does not extend well to incorporate adjustment for confounders. In this situation, the approach using Schoenfeld residuals is more is more suitable for general use when there are several explanatory variables.

In the study of acute lymphoblastic leukaemia (Chapter 5), there was evidence that three variables (age at diagnosis, immunophenotype and secondary malignancy) did not meet the proportional hazard assumption and I needed to use an alternative method to the Cox model. I used the stratified Cox proportional hazards model, which is a direct extension to the Cox model. In the stratified model, I assume that the proportional hazards model holds *within groups* of patients defined by the strata, instead of overall. This method does not provide an estimate of the effect of the explanatory variable used in the stratification on survival.

Formulation of the stratified Cox model

Under the stratified Cox proportional hazards model, the hazard function at time *t* for an individual with explanatory variables X_1, X_2... x_k that are in the stratum *i,* is formulated as:

$$h_i(t) = h_{0i}(t) \exp(\beta_1 x_1 + \beta_2 x_2 .... + \beta_k x_k)$$

where *i* denotes the level of the categorical variable which defines the strata. The hazard ratios are assumed to be the same regardless of stratum, but the baseline hazard can be stratum specific.

Time-dependent variable

In the analyses presented in the acute lymphoblastic study (Chapter 5), I investigated the occurrence of a second primary malignancy after the diagnosis of acute lymphoblastic leukaemia, called secondary malignancy. Because this is a variable that changes over time, it needs to be handled accordingly.

The Cox model can be used when time-dependent variables are present in the model, in which case the explanatory variables in the hazard model are replaced by time-dependent versions, x (*t*), which represent the value of the variable at time *t*. To perform analyses using time-dependent variables, the data need to be arranged appropriately. Individuals who had the event (i.e., secondary neoplasm) will have a row of data pre-event and one row of data post-event. This can be done using the *stsplit* command in Stata. Patients who did not have the event will have only one row of data.

Logistic regression: the odds ratios for early death

In order to examine the association between early death and various sociodemographic and clinical factors, I used logistic regression. Logistic regression models the log odds of binary outcomes for a single or multiple exposures (binary, categorical or continuous explanatory variables).

A. Formulation of the logistic regression for early death

Log odds of early death = $\alpha + \beta 1\ x1 + \beta 2\ x2 + ... \beta k\ xk$

where α = intercept and β is a vector of parameters which represent the associations between the explanatory variables and early death (i.e., 'age group' is a vector of indicators of being in different age groups). The intercept (α) is the log odds when all explanatory variables are at their baseline level. The β parameters are the log odds ratios, which are the increases in the log odds that are associated with a unit increase in exposure.

This model also gives the 95% CI for the odds ratio (OR) and one can perform tests of the null hypothesis that an OR = 1 (log OR = 0), indicating no association between the explanatory variable and the outcome. In the alternative hypothesis, an OR $\neq$ 1, indicates an association between early death and the explanatory variables. Similarly to the Cox models, the hypothesis tests are performed using the Wald test or the likelihood ratio test.

Handling explanatory variable observed for part of the studies

The majority of the variables used in this thesis were available from 1988 to 2011. However, one of the explanatory variables, health insurance status (insurance), was available only from 1996 onwards, when it started to be routinely collected by the California Cancer Registry. To measure the association of insurance and the hazard of death or odds of early death, using Cox regression and logistic regressions respectively, I created 2 extra models using data from 1996 onwards: one containing all explanatory variables but health insurance and another with the explanatory variables including health insurance.

Handling missing dates

Three dates are required to estimate survival: date of birth, date of diagnosis and date of last known vital status (date of death or censoring). Date of birth is not included in the definition of survival time, but is relevant to allocate patients for the estimation of survival by age groups.

It is feasible to impute some missing elements assuming that a possible error will not potentially bias the survival estimates. When there were missing dates in my data, I used an algorithm developed by the CONCORD Working Group[19] to perform imputation. The following dates are considered imputable: day and month of birth, day of diagnosis, and day and month of last vital status (date of death or censoring).

The first step of the imputation process requires the identification of the lower and upper bounds of the period in which the date to be imputed can potentially lie (the imputation period). It is important to pay attention to the

month length (28, 30, 31 days), and, in the case of February, whether it falls in a leap year (29 days). The second step is to identify the middle day of the imputation period as the imputed date. The rational for this is based on the actuarial assumption (uniform distribution of the date during the imputation period), therefore the expected date for the occurrence of an event is the middle day. In the imputation process, day and month of birth and last vital status are imputed first followed by imputation of day of diagnosis.

In the California Cancer Registry, most of the dates were complete (day, month and year). In the datasets I used in this thesis, there was not missing year, missing months of diagnosis and vital status varied from 0.25%–0.60% and 0.01–0.13%, respectively; and missing days of diagnosis and vital status varied from 2.9%–5.1% and 0.40%–0.71%. Therefore, I assume that the imputation of dates performed in my analyses was not sufficient to lead to bias in survival estimates.

Follow-up information is vital for accurate estimation of cancer survival. As discussed in section 4.2.2, the California Cancer Registry conducts intensive active and passive follow-up to provide the more precise follow-up information. Inevitably, during a long-term observation, some patients will have emigrated to another State or country and will be lost to follow-up. However, the proportion of patients who emigrate is usually small and may not influence survival significantly.[249]

Pinheiro et al.[249] investigated the impact of follow-up type and missed deaths on the estimation of cancer survival using SEER data. They found that Hispanics and Asians are more likely to be loss to follow-up than white and black patients. Therefore, survival estimates may be significantly

overestimated in these patients. Considering that the CCR / SEER standard of follow-up information were met and missing last vital status dates were minimal in my datasets, I assume that there were not significant bias due to loss to follow-up in my studies. Moreover, if the survival of Hispanics were overestimated, I would then have an even wider survival gap between white and Hispanic patients.

4.3.4 Methods for adjusting for confounders

In any observational study it is important to adjust for variables that could confound the association between an explanatory variable and the outcome of interest. For a variable to be considered a *confounder*, it needs to: 1) be associated with the exposure 2) be associated with the outcome or disease of interest, 3) should not be in the causal pathway between exposure and outcome.[271]

The Kaplan-Meier estimator does not directly enable adjustment for confounders. However, this can be done by making the Kaplan-Meier plots for an explanatory variable within categories of a confounder. When there is more than one confounder this approach becomes more complicated and may not be efficient due to a small number of individuals in each subgroup. Thus, use of multivariable modelling is usually the best approach to control for confounders. To investigate the extent to which the variables confound each other, I fitted univariable models for each explanatory variable and multivariable models including all the explanatory variables of interest.

4.3.5 Statistical interaction or effect-measure modification

In Epidemiology, the term *interaction* refers to a condition in which "two or more risk factors modify the effect of each other with regard to the occurrence or level of a given outcome". Interaction is also known as "*effect modification*" and needs to be differentiated from *confounding* (described above in section 4.3.2).[271]

For binary variables, *interaction* means that the association of the exposure X on the outcome Y differs depending on whether or not another variable Z (the effect modifier) is present. For ordinal or categorical variables, *interaction* means that the association between the exposure X and the outcome Y varies across levels (stratum) of a third variable Z (the effect modifier).

When more than one predictor is included in the model, it is appropriate to test for interactions between variables. In Stata, the investigation of interaction can be done by adding an interaction term between the categorical variables of interest in the model. We can then compare the models with and without the interaction term using a likelihood ratio test since the models are nested. In this thesis, I tested for interactions between several variables as it is shown in the studies, and found no interactions between the variables tested.

4.3.6 Stata commands

All analyses in this thesis were performed using the statistical software Stata 13.1.

In Stata, the ***stset*** command informs that time-to-event data have been used and this command is used to estimate survival using the Kaplan-Meier approach. Then, many built commands can be employed, including the ***stcox*** command for the survival analysis.

The ***logistic*** command was used to report the odds ratios for early death.

The ***stsplit*** command was used to deal with time-dependent variables.

The likelihood ratio test was performed using the ***lrtes****t* command.

4.4 Potential bias in population-based studies

Many factors may affect survival estimates from population-based studies. These factors may be related to the patient or tumour, as well as to data quality or heath care system characteristics. Study of the distribution of these factors can help to explain differences in survival between different subgroups of cancer patients. However, the magnitude of these factors may be estimated, but they cannot always be controlled for in the survival analysis. Table 4.4 summarises the main factors that influence population-based survival estimates.

4.4.1 Biases due to data quality

The main biases that can occur when estimating survival from population-based studies are secondary to data quality. The principal elements that affect data quality include time since registry's inception, the experience of registry personnel and the availability and quality of different data sources. It is necessary to consider four dimensions of data quality: comparability, completeness, validity and timeliness:[272]

Comparability: in order to compare incidence and survival between registries, regions and countries over time, standardisation of classification, coding and definition of new cases are required.

Completeness: is the "extent to which all incident cancers occurring in the population are included in the registry database". Completeness of ascertainment (or registration) should be as close to 100% as possible, in order to provide incidence rates and survival estimates near to the true value.

Table 4.4: Factors that influence population-based survival estimates. Adapted from Black et al., *IARC Sci Publ* 1998[243]

Data quality (sources of potential bias)
Completeness of ascertainment
Accuracy of recording of the key variables (e.g. date of diagnosis and date of death)
Completeness of follow-up
Timeliness
Death certificate only (DCO) registrations
Host factors
Age
Sex
Race/Ethnicity
Comorbidity
Socio-economic status (SES)
Behaviour (including awareness of cancer symptoms and compliance with treatment)
Tumour-related factors
Extent of disease
Site of tumour (not applicable for leukaemias)
Morphology of tumour
Tumour biology
Health care-related factors
Screening (not applicable for leukaemias)
Diagnostic facilities
Treatment facilities
Quality of treatment
Follow-up care

Validity or accuracy: “the proportion of cases in the dataset with a given characteristic (e.g. morphology code and age) that truly have the attribute.” It depends on the reliability of the sources of information and on the experience of cancer registry personnel to collect code and recode the data.

Timeliness: timeliness of reporting cancer data refers to the “promptness at which a registry can abstract, process and report reliable and complete data”. Some users of cancer data require timely data whenever it is possible. However, the early release of these data from registries can affect the completeness and accuracy of the data.

Bias due to under-ascertainment of incident cases in different populations

I have used standardised high-quality data from the California Cancer Registry. But data quality is expected to vary widely between and within developing and developed countries.

Differential under-ascertainment of incident cases is a main concern. If a substantial number of patients are not recorded in a certain registry area or country, it can artificially increase cancer survival estimates for this area or country. This is particularly true in resource-poor countries since the probability of being registered tends to be correlated to risk factors and the accuracy of diagnostic information.[243] In developing countries incorrect diagnosis of leukaemia is not infrequent since leukaemia symptoms are non-specific and can be mistaken for infectious diseases such as malaria, HIV/AIDS or tuberculosis. Leukaemias can also co-exist with infection and

malnutrition in these children, who may be particularly sick. Acute leukaemia is a disease that generally leads to death in a few weeks or months without treatment. Children living in rural areas of poor countries may die without a diagnosis of acute leukaemia having been made. Consequently, under-reporting of these cases will lead to an over-estimation of survival in this particular population.

On the other hand, if only a random sample of cases of children with acute leukaemia is under-reported (non-differential ascertainment of incident cases), there will not be significant bias in survival estimates. This is, however, unlikely to happen in low- and middle-income countries due to the factors mentioned above.

Bias due to misclassification

Classification of haematologic malignancies has undergone major changes with the publication of the third edition of the International Classification of Diseases for Oncology (ICD-O-3) in 2000.[273] This has led to a revision of the International Classification of Childhood Cancer (ICCC-3).[274] As explained earlier in this thesis (section 2.3.2), ICD-O-3 codes eliminate the artificial difference between lymphoblastic leukaemias and lymphoblastic lymphomas.

A particular concern for international comparisons is that registries may code differently the neoplasms under study. For example, among the non-Hodgkin lymphomas (NHL), precursor T-cell lymphoblastic lymphoma is relatively frequent in children, and is coded 9729/3 in ICD-O-3. However, in the past it was often referred as T-cell NHL without the word “lymphoblastic” or “precursor”. This means that some registries might have coded these cases

as 9591/3 (NHL not otherwise specified) or 9702/3 (mature T-cell NHL). Thus, children with T-cell lymphoblastic lymphoma would be excluded from the survival analyses. In this situation, survival estimates for the respective registry may be over-estimated, since T-cell cases tend to have a worse prognosis than B-cell cases (section 2.5.1).

Potential effect of loss to follow-up and "immortal" cases

An essential requirement for survival analysis is the ascertainment of the vital status of the cancer patients. At the end of the study, each patient should be classified as dead, alive or lost to follow-up.

Complete follow-up can be very difficult to obtain, especially in low- and middle-income countries where death registration may be incomplete, and there is a lack of accuracy, efficacy and timeliness in the process of linkage of incidence and mortality registrations. Matching the incident cases with mortality records in these registries can lead to “immortals”: cancer patients who have died but are still recorded as alive in the registry. “Immortal” cases in the data of a registry can lead to over-estimation of survival.

The direction of bias in the estimation of survival due to loss to follow-up is unpredictable. In low- and middle-income countries, many of the patients lost to follow-up will have died (e.g. due to abandonment of treatment), so data from registries with a high proportion of cases lost to follow-up may be subject to bias with unduly high survival estimates. On the other hand, some patients with a more favourable prognosis might move to another area to receive treatment. If those patients are in fact lost to follow-up but are not

censored from analysis because the fact of their emigration is unknown, survival in the original registry population may be under-estimated.

The impact of loss to follow-up will depend on the proportion of this indicator in each registry. According to the experience of EUROCARE studies, misreporting of vital status up to 4%–5% at 7 or 8 years is likely to occur, but will generally lead to a relatively small impact (less than 1%) on five-year survival estimates,[275] mainly for cancer with relatively high survival,[276] such as for childhood leukaemia.

Death certificate only (DCO) cases

Death certificates are a valuable source of information, providing reports on cancer cases that were not registered when patients were alive. Registries usually trace these cases back in order to confirm whether cancer diagnosis was correct, and to obtain the date of cancer diagnosis. In low- and middle-income countries, death certificates can be absent or of poor quality, with incomplete and/or incorrect information. In these countries, registries can face great difficulties in getting accurate information from doctors and hospitals.

Incident cases that are first identified by the register through death certificates are known as death certificate notification (DCN) cases. When these cases are traced-back and there is no other source of information mentioning cancer rather than death certificates, they are reported as death certificate only (DCO) cases. DCO is then considered the “residuum” of cases after all trace-back procedures have failed to obtain further information on cancer patients. Death certificate initiated (DCI) cases are cancer cases

registered after the trace-back procedures are performed by the registries (Figure 4.5).[277]

Low DCO proportions may be due to the efficiency of case-finding and/or efficiency of track-back procedures, whereas high DCO proportions suggest consistent under-reporting of incident cases. By convention, DCO cases are excluded from survival analysis: since the date of cancer diagnosis is unknown, survival cannot be estimated. This is a potential source of bias.

The proportion of DCO cases in cancer registries acceptable for inclusion in studies that compare survival internationally is subject of debate. The main reason is that DCO proportion is influenced by the availability and quality of death certificates, as well as effectiveness of the registry's matching procedures and its capability to trace-back DCN cases.

In the United States and Canada, only cancer registries with less than 5% of DCO cases are included in *Cancer in North America*.[278] *Cancer Incidence in Five Continents* excludes cancer registries with more than 20% of DCO cases.[272, 277] Thus, registries with more than 20% of DCO cases are usually not eligible for inclusion in survival studies.

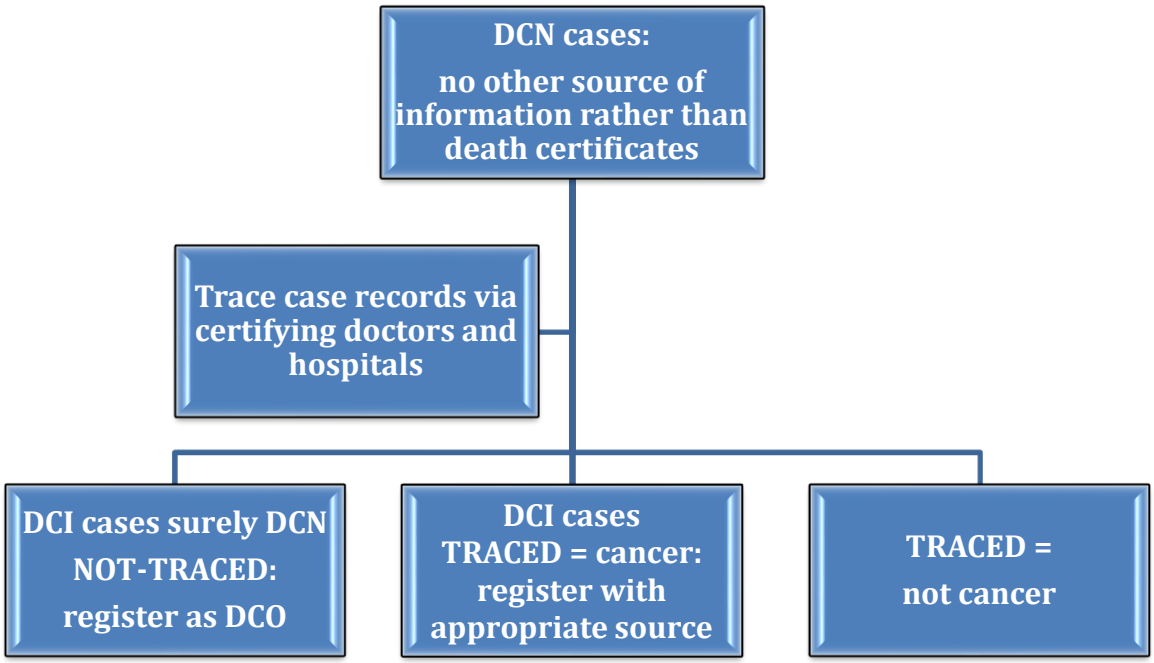

Figure 4.5: The use of death certificates to identify new cases of cancer. Adapted from Bray & Parkin, *Eur J Cancer* 2009[272]

In low- and middle-income countries, in addition to the factors mentioned above, parents of children with leukaemia might be constrained in seeking treatment for their children due to lack of financial resources, lack of education, stigma as well as unavailability of diagnosis or treatment facilities close to their homes. Moreover, children in those settings can be severely ill due to other comorbidities such as malnutrition and co-infection. These children may not be admitted to the hospital for treatment and are less likely to be registered. Cancer registries might receive information on their death but not on the diagnosis or date of diagnosis of leukaemia.

If the proportion of DCO cases is low (<10%), the exclusion of DCOs from survival analysis should not bias survival estimation substantially. However, if the proportion of DCO cases is high, this is likely to introduce a degree of bias. Since the survival of cancer patients registered by DCO is

usually inferior to that of all registered cancer patients,[279] a high proportion of DCO cases will tend to lead to over-estimation of survival.

Berrino et al.[280] examined the impact of DCO cases on survival of patients diagnosed with lung, breast (women) and colorectal cancers, registered in the South Thames Cancer Registry during 1986–1987. They first estimated 5-year overall (crude) survival (%), excluding DCO cases in the usual way. A new data stream became accessible later, allowing the date of diagnosis to be ascertained for many cases that, until that point, had been DCO registrations. The survival estimates were then repeated after inclusion of these cases. When the proportion of DCO cases was higher than 10%, 5-year crude survival was significantly over-estimated. For breast cancer, the inclusion of 11.8% cases in the survival analysis that had previously been DCO cases, reduced the overall survival by 10%. For lung and colon cancers, DCO proportions were 26% and 22%, and their inclusion in the analysis after the date of diagnosis have been obtained, reduced survival estimates by 25% and 20% respectively (Table 4.5). Conversely, if the cases that are under-reported are long-term survivors, survival may then be under-estimated.

Beral and Peto[281] criticised the results of EUROCARE studies,[280, 282-284] arguing that the consistent lower survival observed in the United Kingdom and Denmark compared to other Nordic countries, could be secondary to a mistaken date of diagnosis after tracing-back DCO cases, and an under-reporting of long-term survivors (five years or more). In response, Woods et al.[276] performed a simulation study to estimate the impact of both factors on survival of patients with colon, breast (women) and lung cancers, registered in the National Cancer Registry of England and Wales during 1995–2007.

Failure to report long-term survivors as high as 40% could explain less than half the difference in 1-year survival for breast, lung and colorectal cancers.

Table 4.5: Effect of death certificate only registrations on survival, South Thames Cancer Registry, 1986–1987. Adapted from Berrino et al., *Sci Publ* No 132 1995[280]

	Tumour type		
	Lung	**Breast**	**Colon**
Cancer incidence 1986–1987			
DCO cases	2,670	906	997
Non-DCO cases	7,802	6743	3535
DCO (% of total incidence)	25.5	11.8	22.0
Overall survival (%) at 5 years			
Conventional (without DCO)	6.4	60.1	33.3
Corrected (including DCI)	4.8	54.1	26.6
Reduction in survival (%)	**25**	**10**	**20**

Abbreviations: DCO, death certificate only; DCI, death-certificate-initiated; DCN, death certificate notification**.**

Robinson et al.[285] examined the impact of DCO cases and incomplete registration on survival for 12 anatomic tumour sites, using data from Finnish and Thames (UK) registries. First, they estimated 5-year relative survival excluding DCO cases as usual. Then, adjustment for DCO cases was made, assuming that DCO cases had the same median survival as DCI cases (DCN cases successfully traced) matched by sex, age and tumour sites. Adjustment for incompleteness was also performed. The proportion of DCO cases varied from 1% to 6% in the Finnish registry and was much higher in the Thames registry (between 6% and 32%). After adjustments, considerable changes were observed to survival estimates for tumours sites with a high proportion of DCO cases and/or high percentage of missing cases: adjustment for DCO cases led to substantially lower survival, whereas adjustment for

incompleteness of registration led to substantial over-estimation of survival in the Thames registry. However, the two adjustments resulted in a small effect on 5-year relative survival, even with DCO proportions between 10%–20%, because the increases in survival secondary to adjustment for incompleteness were counteracted by the decrease due to adjustment for DCO cases.

Registries from low- and middle-income countries tend to have higher proportion of DCO cases and incomplete registration, and both can have an important effect on survival estimates. In order to retain data from these countries, it is advisable to limit use of data from registries with up to 20% of DCO cases. Registries with more than 20% of DCO cases should be then excluded. This should be taken into consideration when survival is compared between countries, especially between high-income and low- and middle-income countries. One strategy is to use a sensitivity analysis to examine the changes in survival estimation resulting from varying DCO proportions over a reasonable range. Sensitivity analysis aims to measure the impact of errors – random or systematic – on the estimate's validity.[286]

In the first CONCORD study,[20] DCO proportions were less than 1% in the United States, Canada and Australia, and 0%–5% in most European countries. In Cuba National Cancer Registry, DCO proportions varied from 28% to 60%. Not surprisingly, survival estimates in Cuba were likely to be over-estimated (Cuba had the highest survival estimates for breast and colon cancers comparing to all countries, including the United States, Canada, Japan, European countries and Australia).

4.4.2 Effect of host variables on survival

Age: age at diagnosis is an independent risk factor for outcome for most types of malignancy, and has a strong prognostic effect in survival after childhood and young adult acute lymphoblastic and acute myeloid leukaemias.

Sex: Sex has less marked impact on acute leukaemia survival than age at diagnosis, but most studies show a better prognosis for females compared to males.

Race/ethnicity: Race and ethnicity might influence acute lymphoblastic and acute myeloid leukaemias survival as shown in previous studies.

Comorbidities: Comorbidities such as malnutrition, infections, respiratory and cardiovascular diseases may affect leukaemia survival by increasing the risk of death. Cancer registries, in general, do not provide data on comorbidities. However these factors are less relevant when we analyse survival in the young population in the developed countries. An interesting population-based study recently published in Europe[287] examined the effect of comorbidity and performance status on mortality and complete remission in patients with acute myeloid leukaemia. The authors examine 2,792 patients aged 15–99 years at diagnosis over a 12-year period (2000–2012). Among these patients, the majority did not have any comorbidity (76%), 19% had one comorbidity and only 6% had 2 or more comorbid diseases. Surprisingly, the authors found no evidence of an association between comorbidity and short-term mortality

(death within 90 days of diagnosis) and, if any, just a not statistically significant association with long-term mortality (>90 days to 3 years). The strongest factor associated with both short-and long-term mortality was poor performance status.

Socioeconomic status (SES*):* Population-base registries commonly do not have individual data on socioeconomic status, and researchers use surrogate measures of socioeconomic status at aggregated level.

Patient behaviour: In paediatric oncology, treatment adherence is a process that occurs over a long period of time. Non-adherence to oral agents has been reported to vary from 10%–50%,[288, 289] and it might range from never following the prescription to using drugs irregularly, or using more than was recommended, as well as errors of administration. In the case of acute lymphoblastic leukaemia, it is routine to use oral antineoplastic agents on a daily basis for 2–3 years. This can be particularly challenging in low-resource areas, especially if free treatment is not available for these children.[159] Low adherence to treatment can lead to a worse prognosis and lower survival. This is less significant for acute myeloid leukaemia because treatment is mostly given intravenously.

As discussed in my literature review, abandonment of treatment is considered the major cause of treatment failure amongst children with cancer in developing countries. This is often caused by treatment toxicity, socio-cultural and economic factors.[124, 290] Most of these children who abandon treatment will die because acute leukaemia is a fatal disease when not

appropriately treated. If abandonment of treatment happens after most of treatment is completed, children may be cured or have long-term survival. However, this is unlikely to occur in low-resource areas. High loss to follow-up can be secondary to high level of abandonment of treatment, and this can lead to an over-estimation of survival. The variables level of abandonment of treatment and non-adherence to treatment were not available for my studies.

4.4.3 Influence of tumour-related factors on survival

Acute lymphoblastic leukaemia survival varies according to leukaemia immunophenotype (B- or T-cell), genetic lesions, whether or not central nervous system or testis is involved, or others diseases are associated such as Down syndrome. Likewise, genetic and molecular alteration have prognosis factor for acute myeloid leukaemia, but cannot be accounted for in this thesis.

4.4.4 Impact of health-related factors on survival

Sankaranarayanan et al.[291] estimated survival from a variety of cancer types in 5 developing countries, and compared survival to that of developed countries. The most remarkable differences in survival were found for leukaemias, lymphomas and tumours of testis, malignancies that can be cured or have long-term survival when appropriate treatment is provided

Inequalities in access to care, quality of care and diagnostic limitations result in an enormous survival gap between developing and developed countries. In this thesis, health insurance status and type of hospital were used as a surrogate for access to care.

Acute leukaemia, as well as other types of malignancies, causes considerable morbidity and mortality among children, especially in low- and middle-income countries. Despite its relevance for national and international cancer control strategies, cancer surveillance has been often under-used. In the United Sates, Glaser et al.[292] attributed this fact to an “under-appreciation of the scope of the resources, and a professional mind-set that descriptive epidemiology is simplistic and limited”.

Lately, this scenario has been changing: international collaborative programmes such as EUROCARE[176] and CONCORD[293] have been effectively using cancer surveillance research to produce critical information on cancer survival and thus influence health policy. EUROCARE and CONCORD high-resolution studies aim to provide more specific information such as cancer stage at diagnosis, diagnosis procedures used for staging, and treatment; in order to interpret survival differences in comparative international studies.[294] As noted by Hiatt and Himer,[295] “cancer surveillance research must not only describe the cancer burden and track changes in cancer rates; it also must explain the reasons for observed disparities and trends in cancer burden”. This is the main goal of my thesis.

Chapter 5 Racial/Ethnic and Socioeconomic Disparities in Survival Among Children With Acute Lymphoblastic Leukaemia in California, 1988–2011: A Population-Based Observational Study

5.1 Preamble to research paper 1

In the background chapter and in the literature review, I acknowledged that acute lymphoblastic leukaemia is the most frequent cancer in children and adolescents in the United States, Europe and other developed countries, for which cancer registration data have been standardised, allowing accurate estimates of incidence and survival.

Acute lymphoblastic leukaemia is a severe disease that leads to death within a few months after diagnosis if intensive chemotherapy regimens and adequate supportive care are not provided. Treatment is of long duration (2.5–3 years), expensive and carries a massive burden to patients and their families. If treatment is not appropriate, the patient has a high chance of disease relapse and consequent death.

Despite the dramatic improvement in survival in the last five decades, from universally fatal to potentially curable disease, survival from this malignancy varies widely between and within countries, indicating a need for further investigation of the main factors associated with disease outcome at a population-level.

Due to the high-quality data available from the California Cancer Registry and a large sample of an ethnically and racially diverse population, I

had the opportunity to analyse survival of virtually all patients aged 0–19 years diagnosed with acute lymphoblastic leukaemia (nearly 10,000) during almost 25 years study period (1988–2011), allowing for examination of trends in outcome.

In this population-based study, I simultaneously investigated the influences of neighbourhood socioeconomic status, type of health insurance at time of initial therapy, type of treating facility, and race/ethnicity on survival. My study extends the work of prior studies by considering these factors in addition to those examined previously (age at diagnosis, gender, leukaemia immunophenotype, and calendar period).

In the literature, there is little information on the occurrence of secondary neoplasms in children and adolescents treated for acute lymphoblastic leukaemia.[296-299] Utilizing data from the California Cancer Registry, I was able to provide information on this relevant adverse effect of treatment. I also provided descriptive information on chemotherapy and central nervous system radiation.

My findings identified subgroups with poor survival and highlighted the value of specific information to better understand the causes of lower survival in some groups of children and adolescents with acute lymphoblastic leukaemia, facilitating the eventual development of strategies to decrease survival inequalities.

5.2 Research paper 1

Racial/ethnic and socioeconomic disparities in survival among children with acute lymphoblastic leukemia in California, 1988–2011: a population-based observational study

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Keywords: population-based, survival, childhood, leukemia, race/ethnicity, SES

Abbreviations

ALL	Acute lymphoblastic leukemia
CCR	California Cancer Registry
CCS	California Children's Services
COG	Children's Oncology Group
CI	Confidence interval
CNS	Central nervous system
CRLF2	Cytokine receptor-like factor 2
DCO	Death certificate only
HR	Hazard ratio
ICD-O-3	International Classification of Diseases for Oncology, third edition
NCI	National Cancer Institute
NHAI	Non-Hispanic American Indian
NOS	Not otherwise specified
SEER	Surveillance, Epidemiology and End Results
SES	Socioeconomic status
US	United States

Summary

Background Despite advances in treatment, survival from acute lymphoblastic leukemia (ALL) remains lower among non-White children than White children in the US. We investigated the association of race/ethnicity and socioeconomic status (SES) with survival.

Procedures We analyzed 9,295 Californian children (3,251 Whites, 4,890 Hispanics, 796 Asians, and 358 Blacks) aged ≤19 years diagnosed with a first primary ALL during 1988–2011. We used the Kaplan-Meier method to estimate survival at 1, 5 and 10 years after diagnosis for three calendar periods. Hazard ratios of death for race/ethnicity, SES, and clinical factors were estimated by Cox regression models.

Results Median follow-up time was 7.4 years (range 0–25 years). Over time, survival after ALL improved steadily, but inequalities persisted across races/ethnicities. Five-year survival (95% confidence interval) was 85.0% (83.6–86.2) for White, 81.4% (78.3–84.0) for Asian, 79.0% (77.8–80.2) for Hispanic, and 74.4% (69.4–78.8) for Black children. In multivariable-adjusted models, the hazard of death was increased by 57% among Black, 38% among Hispanic, and 33% among Asian children compared with White children. Patients residing in the lowest SES neighborhoods at diagnosis had a 39% increased risk of death than those living in higher SES neighborhoods.

Conclusion Despite significant improvements in survival, non-White children and children residing in low SES neighborhoods experienced worse survival even after adjusting for potential confounders. Our findings highlight the need to capture specific information on disease biology, treatment and treatment

compliance to better understand the predictors of lower survival in minority and low SES groups.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric neoplasm and the leading cause of death due to disease in children and adolescents aged 1–19 years in the United States (US).[6] Several studies have reported an increase in the incidence of childhood ALL in Europe [24] and the US.[23] Evidence suggests that there may be an inherited genetic predisposition to this disease among different races/ethnicities.[300] Strikingly, genetic factors that increase the susceptibility to ALL appear also to be associated with drug-resistant ALL phenotypes and might, in part, explain the poor survival in certain ethnic groups.[301]

Survival from childhood ALL represents one of the most successful advances in the history of science and medicine. ALL was consistently fatal until the 1950s; however, currently approximately 90% of children can be cured in developed countries.[7] This progress has been attributed largely to the use of effective chemotherapy regimens of variable intensities that are adapted to precise risk stratification and assessment of early treatment response.[7]

Despite the dramatic improvement in the survival of children with ALL in the last four decades, survival has varied widely by race/ethnicity in developed [302] and developing nations.[157] Nonadherence to treatment, lack of access to care, cultural influences, socioeconomic status (SES), and biologic

features have been implicated in these variations.[303] However, the extent to which these factors contribute to survival inequalities remain unclear.

California has the largest and most racially and ethnically diverse population in the US,[304] and it has maintained a statewide high-quality, population-based cancer surveillance system since 1988. In this study, we examined how survival after ALL varied by race/ethnicity, SES and clinical factors in Californian children over a 24-year period. Our population-based study on childhood ALL simultaneously investigates the association of race/ethnicity, neighborhood SES, health insurance, type of treating facility, treatment, and secondary neoplasms as well as factors examined previously (e.g., age, gender, immunophenotype, and calendar period).

Methods

Patients and study design

For this population-based observational study, data were retrieved for children and adolescents aged 0–19 years residing in California when diagnosed with a first, primary ALL from January 1, 1988 through December 31, 2011, and followed for vital status through December 31, 2012. Data were obtained from the California Cancer Registry (CCR), to which all new cases of cancer diagnoses must be reported by State law. The CCR contributes to approximately half of the data in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) and is estimated to include more than 99% of all invasive cancers diagnosed in California. We included the following morphology codes from the *International Classification of Diseases for Oncology*, third edition (ICD-O-3):[305] 9727,

9728, 9729, 9811, 9812, 9813, 9814, 9815, 9816, 9817, 9818, 9835, 9836, and 9837. Among 9,429 eligible patients, 9,295 were included for survival analysis. The following patients were excluded from analysis: 7 reported by death certificate only (DCO), 5 reported by autopsy only, 51 for whom race/ethnicity was unknown, 60 of Non–Hispanic American Indian (NHAI) race/ethnicity for whom the small sample size precluded analysis, and 11 with inconsistent dates of diagnosis or follow-up and/or leukemia classification. ALL was morphologically verified in 99.8% of patients, and the percentage of cases with verified vital status on December 31, 2012, was 87.1%.

Institutional review board (IRB) approval – Ethics approval for human subjects research was obtained from the California 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 HIPPA authorization.

Covariates

Covariates included in the analysis were age at diagnosis (<1, 1–4, 5–9, 10–14, and 15–19 years); gender (male, female); race/ethnicity [Non–Hispanic White (White), Non–Hispanic Black (Black), Hispanic, and Non–Hispanic Asian/Pacific Islander (Asian)]; immunophenotype [categorized as B-cell, T-cell, or not otherwise specified (NOS) according to the morphology codes]; secondary neoplasms; and neighborhood SES. Secondary neoplasm was defined as a new malignancy registered in the CCR after the diagnosis of ALL, following the SEER's multiple primaries rules for hematopoietic diseases.[34] Some types of malignant neoplasms have been associated with

worse prognosis[298] and we have controlled for their occurrence in our analyses. Because information on SES at the individual level is not collected by the CCR, a previously developed neighborhood SES measure[255] was used. It is derived from principal components analysis of seven census indicator variables of SES (education level, proportion unemployed and with a blue collar job, proportion below 200% of federal poverty level, and median household income, rent, and home value). This index is based on data at the level of the census block groups and is considered adequate as a surrogate to SES at individual level,[306] and can capture neighborhood-level factors that may affect cancer incidence and outcomes.[257] SES was divided into quintiles based on the statewide distribution and assigned to patients on the basis of their residence at time of diagnosis. Other covariates included type of insurance at time of initial treatment (private, public, no insurance, or unknown) collected from 1996 onwards; calendar period (1988–1995, 1996–2003, 2004–2011); and type of treating hospital. Because the care provided by specialized pediatric oncologic centers may be different from that provided in general hospitals, we identified children's hospitals and pediatric cancer centers in California by using listings from the Children's Hospital Association[307] and the Children's Oncology Group (COG).[308] These hospitals offer clinical trials sponsored by the COG, which is supported by NCI. On the basis of the cancer reporting facility, patients were classified by whether they had received care at a pediatric cancer center (yes, no). Chemotherapy, radiotherapy and time to chemotherapy were evaluated in descriptive analyses of treatment. They were not included in the statistical model because of changes in the use of central nervous system (CNS) radiation

over time[144] and the widespread use of chemotherapy protocols. Inclusion of treatment in the model did not change the associations observed among race/ethnicity, SES, and survival.

Statistical analyses

We used the chi-square test to compare frequency distributions of sociodemographic and clinical characteristics by race/ethnicity. Follow-up time was defined as the date of diagnosis to the date of death from any cause, or censoring at the end of the study period (December 31, 2012) or last known date of follow-up, whichever came first.

We estimated overall survival at 1, 5, and 10 years for each covariate (except chemotherapy and radiation) and calendar period by the Kaplan-Meier method. The log-rank test was used to compare differences in survival across strata. We used unadjusted and multivariable-adjusted Cox regression models to estimate the hazard ratios (HRs) of death with associated 95% confidence interval (CI).

We tested the proportional-hazards assumption by examining log-log survival plots and confirmed the results by using Schoenfeld residuals. There was evidence that age, immunophenotype, and secondary neoplasms violated the proportional hazard assumption, and these were therefore included as stratification variables in the models. Secondary neoplasm was analysed as a time-dependent variable.

Because information on type of insurance was not routinely collected prior to 1996, we ran three Cox regression models: a model without insurance with all patients, a model without insurance but limited to patients diagnosed

from 1996 onwards, and another model including insurance but limited to patients diagnosed from 1996 onwards. We investigated interactions between racial/ethnic groups and other covariates. Statistical analyses were performed by using the Stata 13 software and a two-sided *P* value<0.05 was considered statistically significant.

Results

Sociodemographic and clinical characteristics

Table 5.1 shows patients and disease characteristics by race/ethnicity. In the 9,295 patients in our cohort, there was a higher percentage of males (58%) than females (42%). More than half the patients (52%) were Hispanic, followed by White (35%), Asian (9%), and Black (4%). The median age at diagnosis was 4 years for Asian, 5 years for White and Hispanic, and 7 years for Black children. By immunophenotype, 60% of patients had B-cell, 12% had T-cell, and approximately 28% had NOS ALL. The proportion of T-cell ALL was significantly higher in Black (23%) than in White (15%), Asian (13%), and Hispanic (10%) children. White and Asian children were more likely to have private insurance (80% and 74%, respectively) than Black and Hispanic children (53% and 40% respectively). Approximately 1.4% of children were diagnosed with secondary neoplasms, of which 58% were solid and 46% were hematopoietic. The use of CNS radiation decreased progressively from 24% in the first time period to 12% in the last period. Chemotherapy was administered to more than 98% of children, of whom at least 95% received chemotherapy within 2 weeks of diagnosis.

Survival

Table 5.2 displays survival probabilities at 1, 5 and 10 years, by sociodemographic and clinical characteristics. Figures 5.1 and 5.2 show survival by race/ethnicity and SES, respectively. The median follow-up time was 7.4 years (range 0–25 years). By the end of the study period, 1,955 study patients died. Survival improved steadily over calendar time but was persistently lower for Black, Hispanic, and Asian children than for White children. Differences in survival were most striking between Black and White children.

Unadjusted and multivariable analyses

In the unadjusted model all variables were associated with significant increased hazard of death. After multivariable adjustment, our analysis revealed that the HRs of death were still significant for race/ethnicity and SES (Table 5.3). The hazard of death was increased by 57% [HR=1.57 (1.26–1.96)] among Black, 38% [HR=1.38 (1.23–1.55)] among Hispanic, and 33% [HR=1.33 (1.12–1.59)] among Asian children compared with White children. Patients residing in the lowest SES neighborhoods were at 39% [HR=1.39 (1.18–1.64)] increased risk of death than those in the higher SES neighborhoods. After controlling for other covariates, the hazard of death was not associated with the type of hospital in which children were treated or with type of insurance for patients diagnosed from 1996 onwards. Insurance minimally attenuated the HRs for race/ethnicity and SES among patients diagnosed from 1996 onwards (Table 5.3). In addition, the inclusion of SES in our model did not substantially change the racial/ethnic differences in survival

that we observed. There were no significant interactions between race/ethnicity, SES, calendar period and other study covariates.

Discussion

In our large population-based study of nearly 10,000 children with ALL, survival for Black, Hispanic, and Asian children was lower than that for White children. The survival differences we observed in our cohort persisted over time and were most marked between Black and White children. In contrast to previous studies reporting that survival of Asian children was similar to[114] or better[155] than for White, Hispanic, and Black children, our study showed that Asian children in California had lower survival than White children with ALL. Our results are consistent with a previous study[302] that also used US population-based data, but we extended their findings by additionally investigating neighborhood SES, secondary neoplasms, type of insurance, treatment and treating facility.

Genetic and non-genetic factors help to explain disparities in cancer survival. Our population-based study allowed the investigation of non-genetic factors and found that neighborhood SES had a significant, independent association with survival, particularly when comparing children residing in the highest and lowest SES neighborhoods. The inclusion of SES in our statistical model did not substantially change the racial/ethnic differences in survival that we observed, suggesting that other factors underlie these survival disparities. Our SES finding is consistent with previous studies of poorer survival among financially deprived populations.[309]

White and Asian children were more likely than Hispanic and Black children to have private insurance, but the type of insurance did not significantly affect survival after ALL after adjustment for other variables. Insurance may have not been associated with survival because, in California, patients younger than 21 years are eligible for California Children's Services (CCS), a State program that offers insurance for chronic and complex diseases and covers all children with cancer with or without insurance. Although the CCS program ensures that all children with ALL have access to care, this may not be sufficient in the long-term for children with low SES. Differences in relapse rates among children from different racial/ethnic groups have been observed. In a study on adherence to oral 6-mercaptopurine during the maintenance phase of ALL treatment, nonadherence was significantly higher among non-White children than White children and it considerably increased relapse rates. Sociodemographic characteristics also played a significant role in adherence to treatment.[309]

Although past evidence suggests that children with ALL treated at specialized pediatric cancer centers had better survival than those at general hospitals,[310] our study did not find survival differences by treating facility. Because the treating facility typically refers to the hospital that initially diagnosed and/or treated the patient, it is possible that some children admitted in nonspecialized pediatric hospitals were later referred to pediatric cancer centers where standardized COG protocols were used, thus confounding our results.

ALL is a lethal disease if treatment is not started promptly. Although the lack of appropriate chemotherapy agents might contribute to the lower

survival in Eastern Europe,[311] our examination of the proportion of children treated with chemotherapy and time from diagnosis to the start of treatment showed that the majority of study patients were treated within the first 2 weeks of diagnosis. However, late diagnosis might have had an adverse effect on outcome. Parents who are undocumented immigrants or of lower SES may wait longer to seek medical care for their children or may do so when the child is already severely sick. Late diagnosis may increase the risk of (early) death[312-314] because patients may develop severe infectious and/or metabolic complications prior to referral to a specialized cancer center.[190] However, we did not have sufficient information to evaluate this possibility.

Our data indicate that the use of prophylactic cranial irradiation has decreased markedly over time, suggesting protocol adherence to the new recommendations for using systemic and intrathecal therapy instead of radiation for children with high-risk CNS relapse. This recommendation aims to prevent late radiation-related complications such as second neoplasms.[299] Infants and older children had significant lower survival than did children aged 1–9 years, supporting findings in previous studies in Europe[5] in the US.[6]

The treatment of childhood leukemia is complex, expensive, and lengthy (2.5–3 years). With modern supportive care, fewer than 10% of deaths among children with ALL are due to therapy-associated toxicity,[315] and disease relapse remains the leading cause of death.[316] Although relapsed ALL is treated with curative intent in the US, the long-term survival of children who relapse is only approximately 25%, even when bone marrow transplant is available.[316] Multiple factors might affect the survival of children with ALL, and

this can be a complex construct involving socioeconomic and cultural variables.[309]

Differences in disease biology may explain, in part, the persistent gap in survival by race/ethnicity. For example, in our study, survival differences were more marked between Black and White children (Figure 5.1; Table 5.3). Intrinsic biologic features may partially explain this observation. Previous studies reported that compared to White children, Black children with ALL had a higher incidence of unfavourable features, including high leukocyte count, higher proportion of T-cell leukemia, chromosome translocations [e.g. t(1,19)], and molecular abnormalities associated with an increased risk of relapse.[317] In contrast, approximately 50% of White children have ALL with favorable genetic features (B-cell ALL), which translate to excellent prognosis.[300] Pui et al.[90] reported that survival rate of Black children receiving intensive risk-based therapy and comprehensive supportive care can be similar to that of White children, thereby reducing the impact of these adverse factors. However, to our knowledge, these results found at a single institution, have not been replicated.

Intrinsic biologic differences may also play an important role in the poor prognosis of ALL among Hispanic children. A recent review[303] of the genomic profiling of ALL associated with susceptibility and outcome among Hispanic children identified a novel subtype of ALL called Philadelphia chromosome-like (Ph–like) ALL among these children. The incidence of Ph-like ALL in Hispanic children is significantly higher (35%) than in non-Hispanic children (7%). Approximately 50% of children with this subtype overexpress the somatic cytokine receptor-like factor 2 (*CRLF2)*.[317] Furthermore, Perez-

Andreu et al.[318] demonstrated that inherited GATA binding protein 3 (GATA3) variants are also overrepresented among Hispanics and increase the susceptibility to Ph-like ALL. The presence of both these variants is associated with a higher risk of relapse among Hispanic children with ALL and may in part explain their poor response to treatment.

Our study has some limitations. Data on specific genetic abnormalities have only been collected by the CCR since 2010. Because of the small size of this group, we could not compare the survival of children on the basis of genetic characteristics. However, this will be of interest in future studies. Most children and adolescents with ALL in California are treated at pediatric cancer centers that use COG protocols, but we do not have information about which patients are treated with these protocols and the intensity of treatment administered. We lacked data on relapse rates, as disease recurrence is not routinely collected by population-based cancer registries.

The strengths of our study include the use of a high-quality population-based dataset, a large sample of an ethnically and racially diverse population, and long period of post-diagnostic observation that allowed us to examine trends in outcome. Our study covered nearly the entire population of children and adolescents diagnosed with ALL in California and provided information on numerous factors such as neighborhood SES, insurance, treatment, treating facility, secondary neoplasm, and immunophenotype as well as age, gender and calendar period.

In summary, despite the remarkable improvement in cure rates after ALL, non-White children and children in low SES neighborhoods have been disproportionally dying even when access to high-quality care is available and

standardized protocols are followed. In the coming years, genomic findings will dramatically change the prognostic classification of ALL. In the era of precision medicine, the value of population-based cancer registries can be improved by collaborating with pediatric oncologists and cancer registries from COG-affiliated hospitals. Capturing specific biologic (e.g., ALL genomic signature, minimal residual disease, blast chromosomal abnormalities, presenting white counts, and NCI risk grouping), and socioeconomic (e.g., treatment compliance) information can help to identify predictors of racial/ethnic differences in treatment failure and guide the development of interventions aimed at improving survival for minority and low SES children with ALL.

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Authorship

Contribution: RA and DYL performed and RK advised on the statistical analyses. DYL, RCR, SLG, RK, RMG, and NMM interpreted the data and drafted and critically reviewed the manuscript. RA and THMK designed the study, interpreted the data, and led the writing and review of the manuscript. All authors read and approved the final manuscript.

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Table 5.1: Sociodemographic and clinical characteristics of children (aged 0–19 years) with acute lymphoblastic leukemia diagnosed from 1988 to 2011 and followed up to 2012 in California, by race/ethnicity

Covariates	Whites N (%)	Blacks N (%)	Hispanics N (%)	Asians N (%)	Total cohort N (%)	*P**
Total	3251 (35)	358 (4)	4890 (52)	796 (9)	9295 (100)	
Age at diagnosis, years						
<1	69 (2.1)	9 (2.5)	158 (3.2)	29 (3.6)	266 (2.9)	
1–4	1468 (45.2)	117 (32.7)	2023 (41.4)	382 (48.0)	3990 (42.9)	
5–9	868 (26.7)	102 (28.5)	1216 (24.9)	194 (24.4)	2382 (25.6)	
10–14	465 (14.3)	74 (20.7)	807 (16.5)	101 (12.7)	1447 (15.5)	
15–19	381 (11.7)	56 (15.6)	686 (14.0)	90 (11.3)	1213 (13.1)	<0.0001
Median	5	7	5	4	5	
Gender						
Male	1911 (58.8)	206 (57.5)	2815 (57.6)	459 (57.7)	5391 (58.0)	
Female	1340 (41.2)	152 (42.5)	2075 (42.4)	337 (42.3)	3904 (42.0)	0.738
Chemotherapy						
No	44 (1.3)	11 (3.1)	79 (1.6)	7 (0.9)	141 (1.5)	
Yes	3207(98.7)	347 (96.9)	4811 (98.4)	789 (99.1)	9154 (98.5)	0.031
CNS radiation						
No	2717 (83.6)	275 (76.8)	4085 (83.5)	687 (86.3)	7764 (83.5)	
Yes	534 (16.4)	83 (23.2)	805 (16.5)	109 (13.7)	1531 (16.5)	0.001
Treatment at a pediatric cancer center						
No	931 (28.6)	131 (36.6)	1571 (32.1)	240 (30.1)	2873 (30.9)	
Yes	2320 (71.4)	227 (63.4)	3319 (67.9)	556 (69.9)	6422 (69.1)	0.001
Leukemia immunophenotype						
T-cell	483 (14.9)	84 (23.4)	464 (9.5)	102 (12.8)	1133 (12.2)	
B-cell	1736 (53.4)	176 (49.2)	3183 (65.1)	490 (61.6)	5585 (60.1)	
NOS	1032 (31.7)	98 (27.4)	1243 (25.4)	204 (25.6)	2581 (27.7)	<0.0001
Secondary neoplasms						
No	3209 (98.7)	356 (99.4)	4838 (98.9)	782 (98.2)	9185 (98.8)	
Yes	42 (1.3)	2 (0.6)	52 (1.1)	14 (1.8)	110 (1.2)	0.223
Socioeconomic status						
1. Lowest 20%	247 (7.6)	96 (26.8)	2067(42.2)	102 (12.8)	2513 (27.0)	
2	532 (16.4)	109 (30.5)	1256 (25.7)	120 (15.1)	2020 (21.7)	
3. Middle 20%	683 (21.0)	66 (18.4)	831 (17.0)	139 (17.5)	1723 (18.5)	
4	847 (26.0)	58 (16.2)	479 (9.8)	200 (25.1)	1585 (17.1)	
5. Highest 20%	942 (29.0)	29 (8.1)	257 (5.3)	235 (29.5)	1463 (15.7)	<0.0001
Calendar period						
1988–1995	1169 (35.9)	104 (29.0)	1162 (23.8)	222 (27.9)	2657 (28.6)	
1996–2003	1093 (33.6)	127 (35.5)	1670 (34.1)	270 (33.9)	3160 (34.0)	
2004–2011	989 (30.4)	127 (35.5)	2058 (42.1)	304 (38.2)	3478 (37.4)	<0.0001
Type of health insurance: limited to cases diagnosed from 1996 onwards (N=6638)						
No insurance	14 (0.7)	9 (3.5)	106 (2.9)	4 (0.7)	133 (2.0)	
Private insurance	1669 (80.1)	135 (53.2)	1493 (40.0)	425 (74.0)	3722 (56.1)	
Public insurance	341 (16.4)	101 (39.8)	1997 (53.6)	128 (22.3)	2567 (38.7)	
Unknown	58 (2.8)	9 (3.5)	132 (3.5)	17 (3.0)	216 (3.2)	<0.0001

Abbreviations: CNS, central nervous system; NOS, not otherwise specified. *Chi-squared test *P*-values.

Table 5.2: Overall survival with 95% confidence intervals for acute lymphoblastic leukemia at 1, 5, and 10 years after diagnosis in children (0–19 years old) in California from 1988 to 2011, by sociodemographic and clinical factors.

Covariates	1-year survival (95% CI)	5-year survival (95% CI)	10-year survival (95% CI)
All children	94.5 (94.0–95.0)	81.2 (80.3–82.0)	77.1 (76.1–78.0)
Age at diagnosis			
<1	76.9 (71.3–81.6)	50.2 (43.7–56.2)	45.7 (39.1–52.1)
1–4	97.9 (97.4–98.3)	89.3 (88.2–90.3)	86.3 (85.1–87.4)
5–9	96.6 (95.8–97.3)	86.2 (84.7–87.6)	80.7 (78.8–82.4)
10–14	91.8 (90.2–93.1)	73.5 (71.0–75.7)	69.0 (66.3–71.5)
15–19	86.3 (84.2–88.1)	60.2 (57.2–63.0)	55.8 (52.6–58.8)
Log-rank test *P*-value<0.00001			
Race/ethnicity			
White	95.8 (95.0–96.4)	85.0 (83.6–86.2)	81.5 (80.0–82.9)
Black	91.8 (88.4–94.2)	74.4 (69.4–78.8)	70.7 (6–75.4)
Hispanic	93.9 (93.2–94.5)	79.0 (77.8–80.2)	74.4 (73.0–75.7)
Asian	94.4 (92.6–95.8)	81.4 (78.3–84.0)	77.4 (74.0–80.4)
Log-rank test *P*-value<0.00001			
Gender			
Male	94.3 (93.7–94.9)	79.5 (78.3–80.6)	75.1 (73.8–76.3)
Female	94.7 (94.0–95.4)	83.5 (82.2–84.7)	79.9 (78.4–81.2)
Log-rank test *P*-value<0.00001			
Leukemia immunophenotype			
B–cell	95.4 (94.8–95.9)	82.7 (81.6–83.7)	77.8 (76.5–79.0)
T–cell	90.8 (88.9–92.3)	73.8 (71.0–76.3)	71.0 (68.0–73.7)
NOS	94.3 (93.3–95.1)	81.1 (79.5–82.6)	77.8 (76.1–79.4)
Log-rank test *P*-value<0.00001			
Calendar period			
1988–1995	93.0 (91.9–93.9)	76.9 (75.2–78.5)	72.8 (71.1–74.5)
1996–2003	94.8 (93.9–95.5)	80.7 (79.3–82.1)	76.7 (75.1–78.1)
2004–2011	95.5 (94.7–96.1)	85.7 (84.3–87.0)	N/A
Log-rank test *P*-value<0.00001			
Socioeconomic status			
1. Lowest 20%	93.5 (92.4–94.4)	77.0 (75.3–78.7)	72.5 (70.5–74.3)
2	94.5 (93.4–95.5)	81.5 (79.6–83.2)	77.8 (75.6–79.6)
3. Middle 20%	94.5 (93.3–95.4)	82.3 (80.3–84.1)	78.4 (76.2–80.5)
4	95.3 (94.1–96.2)	82.2 (80.1–84.1)	78.2 (75.9–80.3)
5. Highest 20%	95.5 (94.3–96.4)	85.4 (83.3–87.1)	81.3 (78.9–81.6)
Log-rank test *P*-value<0.00001			
Treatment at a pediatric cancer center			
No	92.9 (91.9–93.8)	77.0 (75.4–78.6)	73.2 (71.4–74.9)
Yes	95.2 (94.7–95.7)	83.0 (82.0–84.0)	78.9 (77.7–80.0)
Log-rank test *P*-value=0.0014			
Type of health insurance: limited to cases diagnosed from 1996 onwards (N=6638)			
No insurance	93.3 (88.1–96.9)	77.6 (68.9–84.1)	74.2 (64.4–81.6)
Private insurance	96.6 (94.9–96.2)	85.2 (83.9–86.4)	81.8 (80.3–83.2)
Public insurance	94.8 (93.9–96.5)	81.5 (79.9–83.1)	76.3 (74.3–78.3)
Unknown	91.6 (87.0–94.6)	66.2 (59.3–72.2)	63.0 (55.8–69.3)
Log-rank test *P*-value<0.00001			

Abbreviations: CI, confidence interval; NOS, not otherwise specified; N/A, not applicable.

Table 5.3: Unadjusted and multivariable-adjusted hazard ratios and 95% confidence intervals for overall survival in children (0–19 years old) with acute lymphoblastic leukemia in California

Covariates	Death N(%)	Unadjusted HR1 (95% CI) (1988–2011)	Adjusted HR2 (95% CI) (1988–2011)	Adjusted HR3 (95% CI) (1996–2011)	Adjusted HR4 (95% CI) (1996–2011)
Race/ethnicity					
White	568 (29.1)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Black	100 (5.1)	1.78 (1.44–2.20)	1.57 (1.26–1.96)	1.74 (1.31–2.31)	1.72 (1.29–2.28)
Hispanic	1123 (57.4)	1.47 (1.33–1.62)	1.38 (1.23–1.55)	1.43 (1.22–1.68)	1.37 (1.17–1.62)
Asian	164 (8.4)	1.26 (1.06–1.50)	1.33 (1.12–1.59)	1.42 (1.13–1.79)	1.40 (1.11–1.76)
Gender					
Male	1237 (63.3)	1.27 (1.16–1.39)	1.19 (1.09–1.31)	1.20 (1.06–1.35)	1.19 (1.06–1.35)
Female	718 (36.7)	1.0 (Reference)	1.0 (Reference)	1.00 (Reference)	1.00 (Reference)
Socioeconomic status					
1.Lowest 20%	623 (32.3)	1.61 (1.39–1.87)	1.39 (1.18–1.64)	1.40 (1.12–1.75)	1.30 (1.04–2.27)
2.	414 (21.2)	1.29 (1.10–1.51)	1.15 (0.97–1.35)	1.20 (0.95–1.51)	1.15 (0.91–1.44)
3. Middle 20%	339 (17.3)	1.20 (1.02–1.41)	1.13 (0.95–1.33)	1.10 (0.87–1.38)	1.06 (0.84–1.34)
4.	324 (16.6)	1.23 (1.04–1.45)	1.17 (0.99–1.39)	1.22 (0.97–1.54)	1.20 (0.95–1.51)
5. Highest 20%	246 (12.6)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Calendar period					
1988–1995	781 (39.9)	1.66 (1.47–1.87)	1.97 (1.74–2.24)	N/A	N/A
1996–2003	744 (38.1)	1.38 (1.22–1.56)	1.50 (1.33–1.70)	1.52 (1.34–1.73)	1.50 (1.33–1.71)
2004–2011	430 (22.0)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Treatment at a pediatric cancer center					
No	724 (37.0)	1.35 (1.23–1.48)	1.06 (0.96–1.16)	1.05 (0.92–1.19)	1.05 (0.92–1.19)
Yes	1231 (63.0)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Type of health insurance: model limited to cases diagnosed from 1996 onwards (N=6638)					
No insurance	29 (2.5)	1.54 (1.06–2.23)	N/A	N/A	1.22 (0.83–1.89)
Private insurance	583 (49.6)	1.00 (Reference)	N/A	N/A	1.00 (Reference)
Public insurance	487 (41.5)	1.31 (1.16–1.47)	N/A	N/A	1.15 (1.01–1.32)
Unknown	75 (6.4)	2.31 (1.82–2.94)	N/A	N/A	1.77 (1.38–2.26)

Abbreviations: HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified. The multivariable models were adjusted for all variables presented in the table and stratified by age, immunophenotype and secondary neoplasm. HR1: unadjusted model, HR2: adjusted model without insurance, 1988–2011; HR3: adjusted model without insurance, 1996-2011; HR4: adjusted model with insurance, 1996–2011.

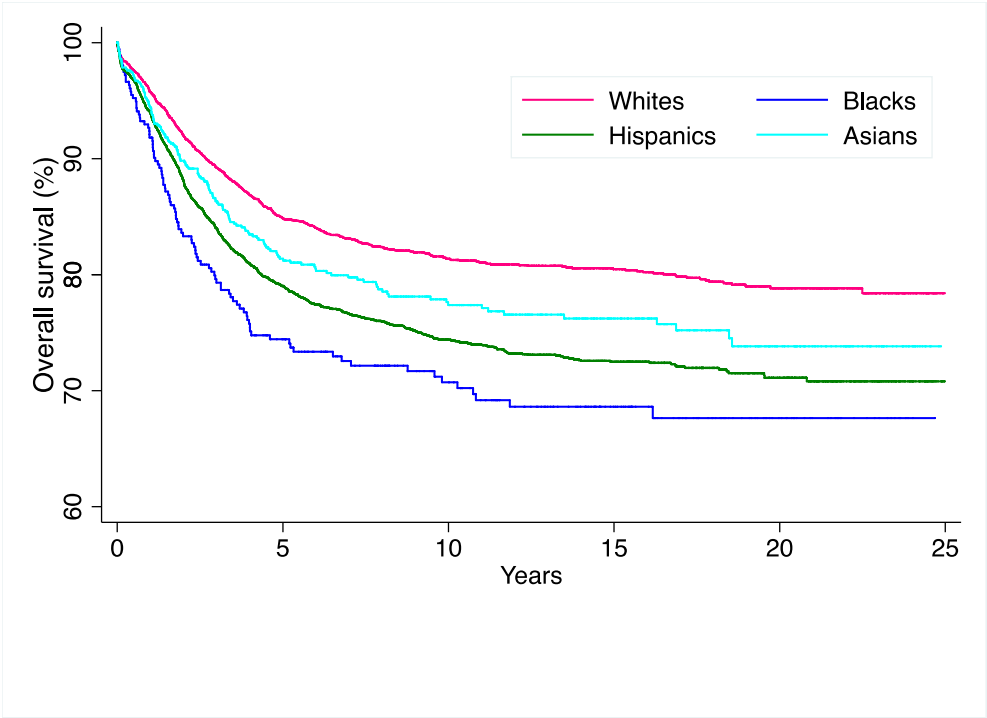

Figure 5.1: Overall survival by race/ethnicity among children (0–19 years old) diagnosed with acute lymphoblastic leukemia in California, 1988–2011

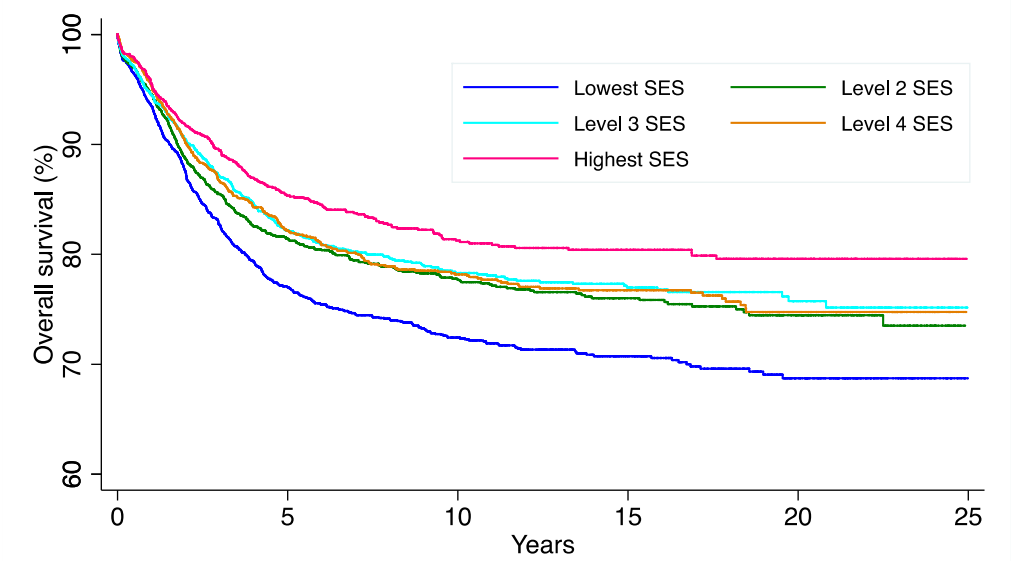

Figure 5.2: Overall survival by socioeconomic status among children (0–19 years old) diagnosed with acute lymphoblastic leukemia in California, 1988–2011

5.3 The incidence of acute lymphoblastic leukaemia in children and adolescents in California

For acute lymphoblastic leukaemia, there is statistical evidence of an increase in annual incidence rates for blacks since 1998 (annual percentage change, APC = 1.8%, 95% CI = 0.6%–3.0%) and Hispanics (APC = 1.1%, 95% CI = 0.6%–1.6%), and borderline evidence of an increase for whites (APC = 0.6%, 95% CI = 0.0%–1.2%). There is not statistical evidence of an increase in incidence for Asian patients (Table 5.4, Figure 5.3).

The incidence rates and APC were calculated using SEER*Stat v.8.3.1 (http://seer.cancer.gov/seerstat/).

Table 5.4: Age-adjusted incidence rates (IR) (per 1,000,000) and annual percentage change of acute lymphoblastic leukaemia, by race/ethnicity in children aged 0–19 years, California, 1988–2011.

	White IR (95% CI)	Black IR (95% CI)	Hispanic IR (95% CI)	Asian IR (95% CI)
Total	36.3 (35.0–37.6)	19.8 (17.8–21.9)	46.3 (45.1–47.7)	31.1 (29.0–33.4)
1988	37.7 (32.0–44.1)	15.8 (7.9–28.3)	37.4 (30.7–45.2)	40.0 (27.4–56.5)
1989	30.5 (25.4–36.3)	13.0 (5.9–24.5)	40.3 (33.4–48.2)	30.5 (20.1–44.5)
1990	33.6 (28.3–39.6)	16.8 (8.6–29.2)	33.5 (27.5–40.4)	35.7 (24.6–50.2)
1991	41.8 (35.9–48.4)	13.7 (6.8–24.7)	45.0 (38.1–52.8)	14.9 (8.1–25.0)
1992	31.0 (25.9–36.8)	21.2 (12.3–34.1)	45.1 (38.3–52.7)	31.8 (21.7–44.9)
1993	37.3 (31.7–43.5)	18.4 (10.3–30.6)	39.9 (33.8–46.9)	30.0 (20.2–42.2)
1994	32.4 (27.2–38.4)	21.4 (12.4–34.4)	46.2 (39.7–53.6)	29.6 (20.1–42.2)
1995	32.3 (27.1–38.2)	14.4 (7.4–25.4)	42.4 (36.3–49.3)	24.2 (15.8–35.5)
1996	33.9 (28.6–40.1)	20.5 (11.9–33.1)	50.4 (43.8–57.8)	36.1 (25.7–49.4)
1997	36.7 (31.1–43.1)	24.9 (15.2–38.6)	46.8 (40.5–53.7)	28.7 (19.5–40.8)
1998	37.4 (31.6–44.0)	24.1 (14.5–37.7)	43.0 (37.0–49.6)	33.5 (23.4–464)
1999	37.3 (31.4–43.9)	15.4 (7.9–26.9)	41.7 (35.9–48.1)	23.4 (15.1–34.5)
2000	38.0 (32.0–44.8)	19.9 (11.4–32.4)	47.8 (41.8–54.6)	26.0 (17.3–37.6)
2001	38.6 (32.5–45.6)	25.8 (15.7–39.8)	42.9 (37.2–49.3)	33.7 (23.7–46.4)
2002	34.1 (28.3–40.7)	16.3 (8.7–28.1)	49.1 (43.0–55.8)	34.4 (24.3–47.2)
2003	33.2 (27.4–39.8)	13.7 (6.6–25.2)	44.9 (39.2–51.3)	34.0 (24.1–46.6)
2004	44.3 (37.5–52.0)	18.7(10.2–31.5)	48.3 (42.3–54.8)	30.6 (21.3–42.5)
2005	35.5 (29.4–42.5)	21.0 (11.7–34.7)	45.4 (39.7–51.7)	35.4 (25.5–47.9)
2006	35.9 (29.7–43.0)	26.2 (15.7–41.0)	50.3 (44.3–56.9)	31.6 (22.2–43.5)
2007	44.0 (37.0–51.9)	25.4 (14.8–40.5)	51.0 (45.0–57.5)	29.2 (20.3–40.6)
2008	36.6 (30.2–43.9)	22.6 (12.9–36.7)	54.2 (48.1–60.9)	36.4 (26.5–48.9)
2009	39.0 (32.3–46.6)	19.9 (10.6–34.0)	52.0 (46.0–58.5)	32.9 (23.5–44.8)
2010	36.3 (29.8–43.7)	28.4 (17.1–44.3)	53.0 (47.0–59.5)	31.8 (22.6–43.4)
2011	40.2 (33.3–48.1)	23.4 (13.4–38.1)	46.1 (40.6–52.3)	31.7 (22.5–43.3)
APC (%) (95% CI)	0.6 (0.0–1.2)	1.8 (0.6–3.0)	1.1 (0.6–1.6)	0.3 (–0.7–1.3)
***p*–value**	0.05	0.01	<0.001	0.56

Abbreviations: APC, annual percentage change; CI, confidence interval; IR, incidence rates.

Patients of American Indian (small numbers) or unknown race/ethnicity were excluded.

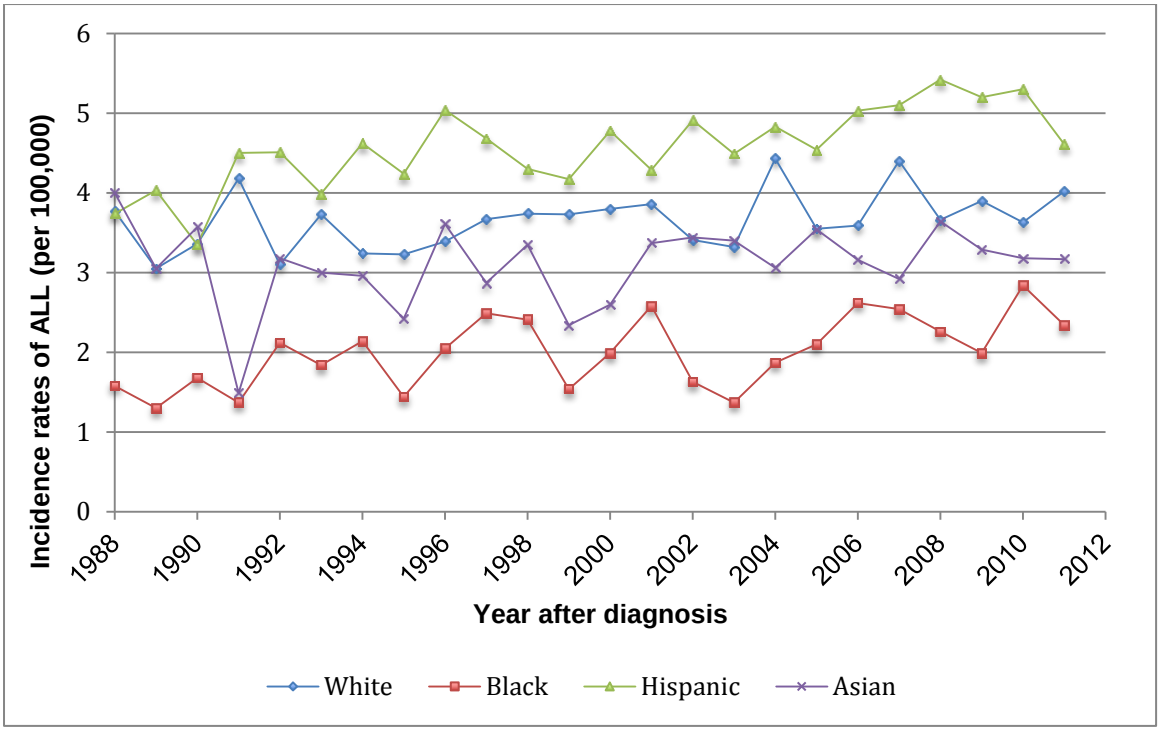

Figure 5.3: Age-specific incidence rates of acute lymphoblastic leukaemia (per 100,000), by race/ethnicity, for patients aged 0–19 years, California, 1988–2011.

Chapter 6 Disparities in Early Death and Survival in Children, Adolescents and Young Adults with Acute Promyelocytic Leukaemia in California

6.1 Preamble to research paper 2

In my literature review, I learned that acute promyelocytic leukaemia was a subtype of acute myeloid leukaemia with a favourable prognosis, and it is currently considered one of the most curable leukaemia subtypes. However, this malignancy is characterised by severe coagulopathy that leads to death within a few days after diagnosis (early death) if treatment including all-*trans* retinoic acid (ATRA) is not promptly initiated as soon as diagnosis of the disease is suspected.

From the results of clinical trials and population-based studies, I observed that there was controversy regarding whether mortality within 30 days of diagnosis of acute promyelocytic leukemia had decreased because of the introduction of ATRA and other factors such as advances in supportive care measures and prompt access to medical care. ATRA was approved by the US Food and Drug Administration in the end of 1995. Using the high-quality data from the California Cancer Registry, I evaluated early death and survival trends before and after the introduction of ATRA.

To my knowledge, this is the first population-based study that examines the association of early death in children, adolescents and young adults with acute promyelocytic leukemia and simultaneously investigates the potential association of health insurance status, race/ethnicity, hospital type, socioeconomic status, as well as age and sex, with disease outcomes. Because recent studies have examined early death in patients aged ≥ 15 years and there is a lack of population-based

studies in young patients with acute promyelocytic leukemia, I investigated early death and survival in patients aged 0–39 years in California over a 25-year period.

Unlike many clinical trials and even some population-based studies, I did not exclude who were not eligible for chemotherapy or those who died within 7 days of diagnosis, increasing the generalizability of my findings. The results of my study highlight the need for strategies aimed to improve access to effective treatment for young patients with acute promyelocytic leukemia, mainly in disadvantaged populations.

6.2 Research paper 2

Disparities in early death and survival in children, adolescents and young adults with acute promyelocytic leukemia in California

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Précis

- During the ATRA era, 30-day mortality and survival improved among children and AYAs with APL, while 7-day mortality remained constant.
- Higher risk of 30-day mortality and worse survival were associated with lack of health insurance (1996–2011) and Hispanic race/ethnicity.

ABSTRACT

Background Findings from clinical trials and population-based studies have differed as to whether mortality within 30 days of diagnosis (early death) of acute promyelocytic leukemia has decreased in the era of all-*trans* retinoic acid (ATRA) and anthracycline-based chemotherapy.

Methods We investigated 7- and 30-day mortality and survival in 772 patients aged 0–39 years when diagnosed with APL during 1988–2011, using data from the California Cancer Registry. We used logistic regression and Cox proportional models to examine the association of early death and survival, respectively, with sociodemographic and clinical factors.

Results Overall 30-day mortality decreased significantly over time, from 26% (1988–1995) to 14% (2004–2011) (*P* = 0.004). In multivariable analysis, the odds of 30-day mortality were 3 times as high during 1988–1995 than 2004–2011 (*P* = 0.001). However, 7-day mortality did not improve over time (*P* = 0.229). When patients who died within 7 days of diagnosis were excluded, 30-day mortality during 1996–2011 was 3%–8%, similar to levels reported in clinical trials. Higher early death and lower survival were associated with lack of health insurance (1996–2011) (early death OR = 2.67, *P* = 0.031) and Hispanic race/ethnicity (early death OR = 2.13, *P* = 0.014). Early death was not associated with age, sex, socioeconomic status or hospital type. Black patients also experienced worse survival.

Conclusions Our findings revealed a decreased 30-day mortality during the ATRA era, but 7-day mortality remained high. Efforts to achieve equal outcomes in young patients with APL should focus on improving access to effective treatment, mainly among uninsured patients and those of Hispanic and Black race/ethnicity.

INTRODUCTION

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) that carries the PML/RAR-α fusion in more than 90% of cases. Bleeding and thrombosis are frequent and can be aggravated by cytotoxic chemotherapy, resulting in early death due mainly to intracranial hemorrhage.[319]

An estimated 600 to 800 new cases of APL (4%–13% of AML cases) occur annually in the U.S., most frequently in adults.[177, 180] While APL was once highly fatal, the addition of all-*trans* retinoic acid (ATRA) to anthracycline-based chemotherapy and the introduction of arsenic trioxide (arsenic) have dramatically improved outcomes; currently, 95%–100% of patients with APL gain complete remission.[209, 220] Moreover, arsenic has become the treatment of choice for relapsed APL after frontline treatment with ATRA and chemotherapy.[320]

ATRA and arsenic rapidly reduce the risk of hemorrhage and should be initiated as soon as APL is suspected.[321] ATRA was approved by the U.S. Food and Drug Administration (FDA) in November, 1995 and arsenic in September, 2000. During the ATRA era, early death has decreased overall, from approximately 20%[193, 195] to 5%–10%.[202] However, early death remains high in the U.S.[22, 213] and Europe,[186] implicating factors other than ATRA.

Because recent studies have examined early death and survival in patients aged ≥15 years[186, 213, 322] and there are few reports of population-based studies in young patients with APL (Supplementary Table S1), we investigated early death and survival in patients in California, diagnosed at ages 0–39 years over a 25-year period, and assessed the association of sociodemographic and clinical factors with these outcomes.

PATIENTS AND METHODS

Patient selection

Data were obtained from the California Cancer Registry, to which reporting is mandatory and completeness of cases is at least 98%.[323] We identified all patients with a first, primary APL diagnosed at age 0 to 39 years during 1988–2011 and followed until December 31, 2012. APL was diagnosed as histology code 9866 in the *International Classification of Diseases for Oncology*, third edition.[305] Of 784 patients identified, 4 were excluded due to missing date of diagnosis and 8 due to unknown or Native American (small subgroup) race/ethnicity. Our study included 772 patients.

Variables

The variables examined for association with APL outcomes were age at diagnosis, categorized as four groups based on progressive decrements in survival[324] (0–9, 10–19, 20–29 and 30–39 years); sex; era of diagnosis according to ATRA approval by the U.S. FDA (pre-ATRA era, 1988–1995; earlier ATRA era, 1996–2003; and later ATRA era, 2004–2011); race/ethnicity (non–Hispanic white [white], non-Hispanic black [black], Hispanic, and Non-Hispanic Asian/Pacific Islander [Asian]); initial care at hospitals affiliated with National Cancer Institute (NCI)-designated cancer centers; type of health insurance at admission (routinely documented starting in 1996) (none, public, private or unknown/not otherwise specified); and neighborhood socioeconomic status (SES) based on block-level census data. Neighborhood SES quintiles based on statewide distribution have been utilized extensively in California.[255]

Information on hospital designation was from the initial reporting facility. There were no data on intensity of treatment or drugs used (conventional genotoxic chemotherapy, ATRA and/or arsenic).

Statistical analysis

We used univariable and multivariable logistic regression to investigate the association of the sociodemographic and clinical factors with 7- and 30-day mortality, through estimation of the odds ratios (ORs) and associated 95% confidence intervals (CIs). We analyzed 30-day mortality with and without patients who died within 7 days. We estimated overall survival (all-cause survival) at 1 and 5 years by using the Kaplan-Meier method, and compared differences in survival across strata for each variable using the log-rank test. We used univariable and multivariable Cox regression models to examine the association of sociodemographic and clinical factors with the risk of death, through estimation of the hazard ratios (HRs) and associated 95% CIs. Schoenfeld residuals were used to assess the proportional hazard assumptions. We tested for interactions between calendar periods, age groups, neighborhood SES and race/ethnicity. All statistical analyses we performed by using the Stata 13 software. A two-sided $P<0.05$ was considered statistically significant.

RESULTS

Approximately 16% of all AML cases in the registry were APL, most of which (79%) were diagnosed during the ATRA era (after 1995). According to death certificates, most patients died of leukemia (n = 228, 90%); a much smaller percentage of patients died of other (n = 17, 7%) or unknown (n = 7, 3%) causes. Fewer than 2% of patients died of complications of APL treatment, such as infection (n = 2), renal dysfunction (n = 1) or heart failure (n = 1). Table 6.1 summarizes patient characteristics.

Early death

Among patients who experienced early death, median age at diagnosis was 29 years; 82 of these patients (11%) died within 7 days and 133 (17%) died within 30 days of diagnosis. Thirty-day mortality decreased significantly over the 3 eras from 26% in 1988–1995 (pre-ATRA) to 16% in 1996–2003 (earlier ATRA era) to 14% in 2004–2011 (later ATRA era) (*P*=0.004, Table 6.1) (Figure 6.1). However, 7-day mortality showed no evidence of a significant decrease. In a multivariable analysis (Table 6.2), the odds of 30-day mortality differed significantly between 1988–1995 and later eras (*P*=0.001), but not between the 1996–2003 and 2004–2011 eras. Hispanic patients had a risk of 30-day mortality approximately twice that of white patients. After 1995, type of health insurance was significantly associated with both 7-day and 30-day mortality; the risk of 30-day mortality was approximately 3 times as high in uninsured as in privately insured patients [OR=2.67 (95% CI: 1.10–6.52)]. Early death was not found to differ significantly between patients with private vs. public insurance (*P* = 0.243).

When patients with 7-day mortality (*n* = 82) were excluded from analysis, 30-day mortality decreased from 15% during 1988–1995 to 8% during 1996–2003 and 3% during 2004-2011 (*P* < 0.0001; data not shown). There was no evidence of interactions between any variables.

Survival

During 0 to 25 years of follow-up (median in entire cohort, 4.4 years), 33% of patients (n = 252) died. Five-year survival increased from 46.7% during 1988–1995 to 70.1%

during 1996–2003 and 77.3% during 2004–2011 ($P < 0.0001$, Table 6.1). Based on the log-rank test, a lower survival estimate was significantly associated with earlier period of diagnosis, male sex, older age at diagnosis, and lack of health insurance (Table 6.1). In univariable analyses, survival was lower in Hispanic and black vs. white patients and uninsured vs. insured patients. In multivariable models, the 1988–1995 era, black/Hispanic race/ethnicity and lack of health insurance remained significantly associated with the hazard of death (Table 6.3). There was no evidence of a difference in HR between patients with private vs. public insurance ($P = 0.999$). There was no evidence of violation of the Cox proportional hazard assumptions or of interactions between any variables.

When we excluded patients who died within 30 days of diagnosis in 1996–2011, 5-year survival increased from 77.8% (95% CI: 70.7%–83.3%) to 88.8% (95% CI: 82.4%–93.0%) among patients aged 0–19 years, and from 72.5% (95% CI: 67.8%–76.6%) to 86.3% (95% CI: 81.9%–89.7%) among patients aged 20–39 years (data not shown).

DISCUSSION

In our population-based study spanning 25 years, 30-day mortality decreased significantly after 1995, coinciding with the introduction of ATRA and guidelines recommending aggressive blood product support and intensive infection prophylaxis and treatment for suspected APL. Nevertheless, 30-day mortality remained higher than that observed in non-APL subtypes of AML,[325] and 7-day mortality did not improve over time. Our findings suggest that factors other than ATRA contributed to early death; these may include the timing of diagnosis or chemotherapy, hospital availability of ATRA/arsenic during the critical 2–3 days after diagnosis, adequate

blood products and infection prophylaxis and treatment. A recent study of randomly selected hospitals in the U.S. found that less than half had ATRA, and one of the main barriers to availability was the absence of ATRA on their formularies.[326]

Patients who suffered early death probably lacked early access to effective treatment and/or were too ill when admitted; ten patients in this study died on the day of diagnosis. The FDA's approval of ATRA (and later, arsenic) may not have resulted in the wide or timely availability of these drugs across all California hospitals.

Moreover, despite the great effectiveness of ATRA and arsenic, treatment may cause severe complications that should be recognized and treated promptly, such as differentiation syndrome. Differentiation syndrome occurs in about 2%–31% of patients receiving induction therapy and can mimic other severe complications, such as pulmonary hemorrhage, renal dysfunction and heart failure.[215] Because of the abrupt presentation and potential gravity of differentiation syndrome, preemptive use of corticosteroids has been proposed.[216] The syndrome may be promoted by delaying chemotherapy after ATRA,[327] and delaying ATRA itself for more than 2 days may increase the risk of fatal hemorrhage.[222] These findings confirm the importance of early diagnosis, rapid intensive treatment and adequate supportive care.

Importantly, we found that uninsured patients had a higher risk of early death and lower survival estimates than those with private and public insurance, suggesting lack of adequate access to care. Our results are consistent with a previous report of worse survival in uninsured vs. insured AYAs.[245] Wider insurance coverage is likely to provide better outcomes for these patients. Additionally, early death was higher among Hispanic patients, and survival was lower among black and Hispanic patients, than those among white patients. Similar findings have been reported in children with acute lymphoblastic leukemia (ALL),[155, 328] children with AML (excluding APL)[329] and

adults with AML (including APL).[322] To provide effective and sustainable treatment to patients with APL – a severe but highly curable disease – efforts should also address the social contributors to health inequity,[330] such as poverty, inadequate access to transportation, and lack of education resources.

In general, population-based studies,[22, 213] such as ours, show a greater proportion of early death than do multi-institutional protocols. The differing findings may reflect the exclusion of patients who died during the first week or were too ill for chemotherapy in prior studies.[331] In our study, when we excluded deaths within 7 days, we found 30-day mortality during the ATRA era to approximate that in clinical trials.[202, 208] Similarly, when we excluded patients who died within 30 days of diagnosis, 5-year survival was close to that reported in multi-institutional trials in children and AYAs.[206, 332] These observations suggest that selection bias may contribute to the differences in reported survival and early death between most clinical trials and population-based studies.

Our study had several limitations. Hospital designation was limited to the location of initial care at the reporting facility, so it is possible that some patients diagnosed at one type of facility were subsequently treated at another. However, 92% of our patients received at least part of their treatment at this hospital, suggesting that our findings were not substantially influenced by this factor. We also lacked data on patients' risk classification at diagnosis, laboratory data, and blood products administered. Although this information would likely have contributed additional important findings, disease outcomes such as early death and survival are of paramount concern.

Survival is a measure of the cancer burden and the health system effectiveness and plays a key role in the development of health policies.[19] Our large

California APL cohort allowed us to compare early death and survival across treatment eras and investigate sociodemographic factors associated with outcome. To our knowledge, this is the first population-based study to investigate the association of race/ethnicity with early death and survival in children with APL and to consider the association of outcome with health insurance, hospital type, age, sex, treatment era and neighborhood SES. Further, unlike previous population-based studies,[22, 213, 325] we were able to assess 7-day mortality.

In conclusion, our findings indicate a true reduction of 30-day mortality among children and AYAs with APL in California, suggesting adherence to modern therapeutic strategies. However, 7-day mortality remained high, suggesting that factors other than ATRA played a role in early death. We identified subgroups of patients vulnerable to early death and reduced survival, including the uninsured and Hispanic patients. Black patients also experienced worse survival. To improve outcomes among young patients with APL, efforts should focus on improving access to effective treatment, mainly among uninsured patients and those of Hispanic and Black race/ethnicity.

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Authorship contributions

RA performed and RHK advised on the statistical analyses, RCR, RHK and BCM interpreted the data and drafted and reviewed the manuscript. RA and THMK

designed the study, interpreted the data, and led the writing and review of the manuscript. All authors read and approved the final manuscript.

Institutional Review Board (IRB) approval – Ethics approval for human subjects 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 HIPAA authorization

Table 6.1 Patient characteristics, early mortality, and overall survival

Characteristic	*N* (%)	7-day mortality (%)	*P*[a]	30-day mortality (%)	*P*[a]	1-year OS (%)	5-year OS (%)	*P*[b]
Total	772 (100)	82 (11.0)		133 (17.2)		78.0 (74.9-80.8)	68.1 (64.6-71.4)	
Calendar period								
1988–1995 (pre-ATRA)	163 (21.1)	22 (13.5)		42 (25.8)		61.7 (53.7-68.7)	46.7 (38.9-54.2)	
1996–2003 (earlier ATRA era)	266 (34.5)	22 (8.3)		43 (16.2)		78.9 (73.5-83.4)	70.1 (64.2-75.2)	
2004–2011 (later ATRA era)	343 (44.4)	38 (11.1)	0.229	48 (14.0)	0.004	85.1 (80.9-88.5)	77.3 (72.1-81.9)	<0.0001
Age at diagnosis, years (Median=27 y)								
0–9	50 (6.5)	2 (4.0)		4 (8.0)		84.0 (70.5-91.2)	71.8 (57.1-82.3)	
10–19	172 (22.3)	17 (9.9)		26 (15.1)		81.4 (74.7-86.5)	69.8 (62.1-76.2)	
20–29	225 (29.1)	27 (12.1)		38 (16.9)		79.9 (74.0-84.6)	73.2 (66.7-78.6)	
30–39	325 (42.1)	36 (11.1)	0.396	65 (20.0)	0.152	74.0 (68.9-78.5)	63.1 (57.4-68.3)	0.023
Race/ethnicity								
White	256 (33.2)	20 (7.8)		32 (12.5)		82.8 (77.6-86.9)	72.2 (66.1-77.4)	
Black	45 (5.8)	7 (15.6)		9 (20.0)		73.3 (57.9-83.9)	56.6 (40.6-69.9)	
Hispanic	388 (50.3)	46 (12.4)		79 (20.4)		74.9 (70.2-87.6)	66.5 (61.4-71.1)	
Asian	83 (10.7)	9 (12.1)	0.266	13 (15.7)	0.070	80.6 (70.2-87.6)	69.2 (57.5-78.3)	0.068
Sex								
Male	391 (50.7)	51 (13.3)		77 (19.7)		75.0 (70.4-79.0)	63.1 (57.8-67.8)	
Female	381 (49.3)	31 (8.7)	0.028	56 (14.7)	0.066	81.1 (76.8-84.7)	73.2 (68.3-77.4)	0.005
Initial care at hospitals affiliated with NCI-designated cancer centers								
Yes	155 (20.1)	11 (7.1)		20 (12.9)		81.2 (74.0-86.5)	73.1 (65.2-79.6)	
No	617 (79.9)	71 (11.4)	0.120	113 (18.3)	0.111	77.2 (73.7-80.3)	66.8 (62.8-70.5)	0.078
Neighborhood socioeconomic status (quintile)								
1. Lowest 20%	216 (28.0)	26 (12.2)		42 (19.4)		75.3 (69.0-80.5)	66.3 (59.4-72.3)	
2.	168 (21.8)	24 (14.0)		35 (20.8)		74.9 (67.5-80.8)	66.5 (58.6-73.3)	
3. Middle 20%	151 (19.6)	12 (7.8)		24 (15.9)		78.8 (71.3-84.5)	66.9 (58.5-74.0)	
4.	128 (16.6)	13 (10.2)		19 (14.8)		81.2 (73.3-87.0)	73.1 (64.2-80.1)	
5. Highest 20%	109 (14.1)	7 (6.4)	0.187	13 (11.9)	0.275	83.5 (75.1-89.2)	70.0 (59.9-77.9)	0.425
Health insurance (only patients diagnosed in 1996–2011; n = 609)								
None	45 (7.4)	14 (31.8)		19 (42.2)		53.1 (37.6-66.4)	50.6 (35.2-64.2)	
Public	212 (34.8)	16 (7.4)		23 (10.9)		86.8 (81.4-90.7)	77.2 (70.6-82.5)	
Private	294 (48.3)	27 (9.2)		45 (15.3)		82.0 (77.1-85.9)	74.4 (68.8-79.1)	
Unknown/Not otherwise specified	58 (9.5)	3 (5.1)	<0.0001	4 (6.9)	<0.0001	91.2 (80.2-96.3)	79.2 (65.5-88.0)	0.0001

Abbreviation: ATRA, all-trans retinoic acid. [a]Chi-squared P-value for testing whether early death differs among groups for each covariate. [b] Log-rank P-value comparing differences in survival across strata for each variable. ‡ Three patients were excluded due to missing day of diagnosis.

Table 6.2 Relation of sociodemographic and clinical factors to 30-day mortality

Factor	Unadjusted OR1 (95%CI) (1988–2011)	Adjusted OR2 (95% CI) (1988–2011)	Adjusted OR3 (95%CI) (1996–2011)	Adjusted OR4 (95% CI) (1996–2011)
Calendar period				
1988–1995 (pre-ATRA)	2.18 (1.37–3.46)	3.01 (1.66–5.46)	N/A	N/A
1996–2003 (earlier ATRA era)	1.20 (0.77–1.87)	1.39 (0.80–2.43)	1.41(0.81–2.46)	1.30 (0.74–2.30)
2004–2011 (later ATRA era)	1 (base)	1 (base)	1 (base)	1 (base)
Sex				
Male	1.42 (0.97–2.07)	1.21 (0.76–1.96)	1.22 (0.70–2.13)	1.18 (0.67–2.08)
Female	1 (base)	1 (base)	1 (base)	1 (base)
Age at diagnosis (years)				
0–9	1 (base)	1 (base)	1 (base)	1 (base)
10–19	2.06 (0.69–6.22)	1.90 (0.54–6.74)	1.78 (0.40–7.95)	2.01 (0.44–9.18)
20–29	2.36 (0.80–6.95)	1.83 (0.52–6.42)	1.67 (0.38–7.38)	1.72 (0.38–7.78)
30–39	2.90 (1.01–8.35)	2.48 (0.73–8.45)	2.61 (0.61–11.1)	2.61 (0.60–11.4)
Race/ethnicity				
White	1 (base)	1 (base)	1 (base)	1 (base)
Black	1.75 (0.77–3.97)	1.82 (0.63–5.20)	2.48 (0.72–8.51)	2.37 (0.68–8.31)
Hispanic	1.79 (1.14–2.79)	2.13 (1.16–3.89)	2.20 (1.04–4.63)	2.23 (1.01–4.92)
Asian	1.3 (0.65–2.61)	1.35 (0.56–3.26)	1.11 (0.36–3.51)	1.24 (0.39–3.87)
Neighborhood socioeconomic status (quintiles)				
1. Lowest 20%	1.80 (0.92–3.52)	1.03 (0.44–2.44)	0.83 (0.28–2.52)	0.87 (0.27–2.80)
2.	1.91 (0.96–3.79)	1.08 (0.46–2.53)	0.99 (0.33–2.92)	1.03 (0.33–3.20)
3. Middle 20%	1.38 (0.67–2.84)	0.93 (0.39–2.23)	0.88 (0.29–2.72)	0.93 (0.29–3.01)
4.	1.30 (0.61–2.77)	0.81 (0.32–2.02)	0.79 (0.25–2.53)	0.83 (0.25–2.72)
5. Highest 20%	1 (base)	1 (base)	1 (base)	1 (base)
Initial care at hospitals affiliated with NCI-designated cancer centers				
Yes	1 (base)	1 (base)	1 (base)	1 (base)
No	1.53 (0.92–2.55)	1.07 (0.57–2.00)	1.30 (0.62–2.72)	1.19 (0.55–2.56)
Health insurance (limited to patients diagnosed in 1996–2011; n=609)				
None	3.91 (2.01–7.62)	N/A	N/A	2.67 (1.10–6.52)
Public	0.66 (0.39–1.13)	N/A	N/A	0.66 (0.32–1.33)
Private	1 (base)	N/A	N/A	1 (base)
Unknown/NOS	0.40 (0.14–1.17)	N/A	N/A	0.22 (0.06–0.79)

Abbreviations: OR, odds ratio; CI, confidence interval; NCI, National Cancer Institute.
All multivariable comparisons were adjusted for chemotherapy (Y/N) and all variables in the table unless otherwise noted. OR1: unadjusted model (1988–2011), OR2: adjusted model without insurance (1988–2011), OR3: adjusted model without insurance (1996–2011), OR4: adjusted model with insurance (1996–2011)

Table 6.3 Relation of sociodemographic and clinical factors to the hazard of death

Factor	Death *n* (%)	Unadjusted HR1 (95% CI) (1988–2011)	Adjusted HR2 (95% CI) (1988–2011)	Adjusted HR3 (95% CI) (1996–2011)	Adjusted HR4 (95% CI) (1996–2011)
Calendar period					
1988–1995 (pre-ATRA)	94 (37.3)	2.79 (2.04–3.80)	2.84 (2.06–3.91)	N/A	N/A
1996–2003 (earlier ATRA era)	86 (34.1)	1.39 (1.01–1.90)	1.39 (1.01–1.91)	1.43 (1.04–1.98)	1.40 (1.01–1.94)
2004–2011 (later ATRA era)	72 (28.6)	1.0 (base)	1.0 (base)	1.0 (base)	1.0 (base)
Age at diagnosis, years					
0–9	14 (5.6)	1.0 (base)	1.0 (base)	1.0 (base)	1.0 (base)
10–19	52 (20.6)	1.14 (0.63–2.05)	1.07 (0.58–1.96)	1.13 (0.51–2.52)	1.20 (0.54–2.67)
20–29	60 (23.8)	1.03 (0.58–1.85)	0.99 (0.54–1.81)	0.98 (0.44–2.16)	0.96 (0.43–2.14)
30–39	126 (50.0)	1.56 (0.90–2.72)	1.43 (0.80–2.53)	1.82 (0.85–3.88)	1.83 (0.85–3.93)
Race/ethnicity					
White	73 (29.0)	1.0 (base)	1.0 (base)	1.0 (base)	1.0 (base)
Black	20 (7.9)	1.79 (1.09–2.93)	1.81 (1.08–3.03)	1.97 (0.98–3.96)	1.80 (0.89–3.62)
Hispanic	134 (53.2)	1.33 (1.00–1.77)	1.48 (1.08–2.02)	1.38 (0.90–2.12)	1.31 (0.84–2.03)
Asian	25 (9.09)	1.11 (0.70–1.75)	1.21 (0.76–1.91)	1.11 (0.58–2.12)	1.12 (0.58–2.15)
Sex					
Male	145 (57.5)	1.42 (1.11–1.83)	1.27 (0.98–1.64)	1.52 (1.10–2.11)	1.50 (1.08–2.07)
Female	107 (42.5)	1.0 (base)	1.0 (base)	1.0 (base)	1.0 (base)
Neighborhood socioeconomic status (quintile)					
1. Lowest 20%	75 (29.8)	1.24 (0.82–1.86)	0.90 (0.57–1.41)	1.02 (0.54–1.94)	0.98 (0.51–1.89)
2.	58 (23.0)	1.20 (0.79–1.83)	0.94 (0.60–1.46)	1.01 (0.53–1.90)	1.00 (0.53–1.90)
3. Middle 20%	52 (20.6)	1.15 (0.75–1.77)	0.93 (0.60–1.46)	0.95 (0.50–1.82)	0.94 (0.49–1.80)
4.	33 (13.1)	0.86 (0.53–1.39)	0.72 (0.44–1.18)	0.76 (0.38–1.51)	0.75 (0.37–1.49)
5. Highest 20%	34 (13.5)	1.0 (base)	1.0 (base)	1.0 (base)	1.0 (base)
Initial care at hospitals affiliated with NCI-designated cancer centers					
Yes	41 (16.3)	1.0 (base)	1.0 (base)	1.0 (base)	1.0 (base)
No	211 (83.7)	1.35 (0.97–1.88)	1.07 (0.75–1.52)	1.31 (0.83–2.06)	1.26 (0.79–1.99)
Health insurance (only patients diagnosed 1996–2011; n=609)					
None	22 (13.9)	2.57 (1.59–4.14)	N/A	N/A	2.00 (1.20–3.31)
Public	49 (31.0)	0.91 (0.63–1.31)	N/A	N/A	1.00 (0.67–1.48)
Private	74 (46.)	1.0 (base)	N/A	N/A	1.0 (base)
Unknown/NOS	13 (8.2)	0.82 (0.46–1.48)	N/A	N/A	0.64 (0.35–1.17)

Abbreviations: HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; NCI, National Cancer Institute.
All multivariable comparisons were adjusted for chemotherapy (Y/N), and all variables in the table unless otherwise noted.
HR1: unadjusted model (1988–2011), HR2: adjusted model without insurance (1988–2011), HR3: adjusted model without insurance (1996–2011); HR4: adjusted model with insurance (1996–2011).

Table S 6.1 Consecutive reports of early death after diagnosis of acute promyelocytic leukemia, 1990–2014

First Author	*N*	Period	Age, y	Early death	
				Definition	Percentage
Rodeguiero, F[195]	268	1984–1987	7–78	Death within 10 days after starting chemotherapy	9.4% died of hemorrhagic events and 3.2% of other causes (pre-ATRA era)
Fenaux, P[196]	101	1991–1992	6–67	Death during chemotherapy or ATRA, or during post-chemotherapy aplasia, without evidence of resistant leukemia	9.0% in the ATRA group , 8.0% in the chemotherapy group, (ATRA increased event-free survival)
Estey, E[197]	43	1991–1995	13–80	Death during induction therapy	18.6%
Tallman, MS[198]	346	1992–1995	1–81	Death within 28 days of diagnosis	12.4%
Mandelli, F[199]	240	1993–1996	2–73	Death during induction therapy	5%
Di Bona, E[202]	622	1989–1997	1–74	Hemorrhagic death during the first 10 days of treatment	3.8% in study A (idarubicin + ATRA) 7.3% in study B (idarubicin alone)
Fenaux, P[200]	439	1993–1996	≤ 77	Death during induction with ATRA, without evidence of resistant leukemia	7.0%
Sanz, MA[201]	123	1996–1998	1–74	Death during induction therapy or post-chemotherapy aplasia	9.8%
Lengfelder, E[203]	51	1994–1999	16–60	Death during induction phase before recovery from chemotherapy-related myelosuppression	8.0%
Mann, G[204]	44	1993–2002	1–16	Death within 6 weeks of diagnosis	4.5% (ATRA group), 32% (control group)
Asou, N[205]	369	1992–1997	15–86	Death within 28 days after start of chemotherapy	8.0%
Testi, AM[206]	107	1993–2000	1–17	Death within 34 days of diagnosis	3.7%
Schlenk, RF[221]	82	1995–2003	16–60	Death <7 days after completion of the first induction therapy or death during double induction therapy	12%
Yanada, M[208]	279	1997–2002	15–70	Early hemorrhagic death	3.2% (ATRA for all patients)
Derolf, AG[210]	111	1993–2005	All ages	Death within 30 days of diagnosis	25% during 1993–1999, 18% during 2000–2005
Lo-Coco, F[9]	642 453	1993–2000 2000–2006	18–≤ 61	Death within 45 days of induction treatment with ATRA and idarubicin (AIDA)	5.5% in AIDA-0493[1], 5.6% in AIDA-2000[2]
Lehman, S[186]	105	1997–2006	≥16	Death within 30 days of diagnosis	29.0% (35.0% of patients received no ATRA)
Park, JH[22]	1,400	1992–2007	All ages	Death within 30 days of diagnosis	17.3%
Iland, HJ[209]	124	2004–2009	>1	Death within 36 days of ATRA induction therapy	3.2%
McClellan, JS[213]	70	1997–2009 1977–2007	≥15 19–93	Death within 7 or 30 days from the start of chemotherapy Death within 30 days of diagnosis	18.6% (7 days) and 26.0% (30 days) 20.0%
Altman, JK[222]	204	1992–2009	1–85	Death within 30 days of presentation to medical care	11.0%
Fisher, BT[21]	163	1999–2009	All ages	Death during induction, within 7 and 30 days of admission	4.3% (7 days), 6.1% (30 days)

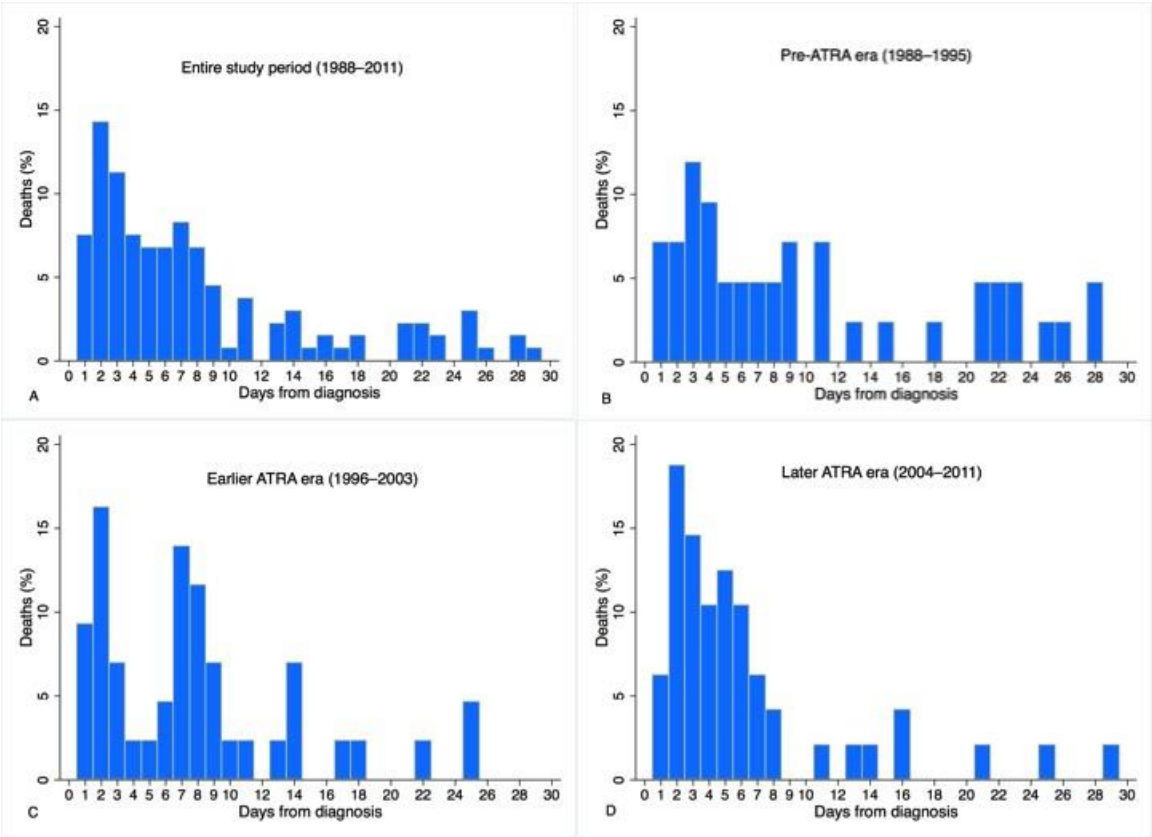

Figure 6.1: Early death from acute promyelocytic leukemia in California, after diagnosis at age 0–39 years. A. Entire study period (1988–2011), B. Pre-ATRA era (1998–1995), C. Earlier ATRA era (1996–2003), D. Later ATRA era (2004–2011). Ten patients who died on the day of diagnosis were considered to have a survival time of 1 day.

6.3 The incidence of acute promyelocytic leukaemia in children, adolescents and young adults in California

For acute promyelocytic leukaemia, there is statistical evidence of annual increase in incidence rates since 1988 for whites (annual percentage change, APC = 4.3%, 95% CI = 2.9%–5.7%) and Hispanics (APC = 4.0%, 95% CI = 1.9%–6.1%). There is no statistical evidence of an increase in incidence for Asian patients (APC = 0.8%, 95% CI = -2.3%–4.1%). It was not possible to estimate the APC for blacks due to the small number of cases (Table 6.4). The incidence rates and APC were calculated using SEER*Stat v.8.3.1 (http://seer.cancer.gov/seerstat/).

Table 6.4: Age-adjusted incidence rates (per 1,000,000) and annual percentage change of acute promyelocytic leukaemia, by race/ethnicity in children aged 0–39 years, California, 1988–2011.

	White IR (95% CI)	Black IR (95% CI)	Hispanic IR (95% CI)	Asian IR (95% CI)
Total	1.3 (1.1–1.4)	1.3 (1.0–1.8)	2.1 (1.9–2.3)	1.4 (1.1–1.8)
1988	0.8 (0.4–1.6)	0.6 (0.0–3.7)	0.6 (0.1–1.8)	0.6 (0.0–3.4)
1989	0.9 (0.4–1.8)	1.5 (0.2–5.2)	0.8 (0.2–1.8)	0.5 (0.0–2.9)
1990	0.6 (0.2–1.4)	0.5 (0.0–3.3)	0.8 (0.3–1.9)	0.6 (0.0–3.0)
1991	0.7 (0.3–1.5)	1.5 (0.2–5.1)	1.2 (0.5–2.4)	2 (0.5–5.1)
1992	1.0 (0.5–1.9)	0.8 (0.0–3.9)	0.8 (0.2–1.9)	1 (0.1–3.5)
1993	1.0 (0.5–1.9)	1.9 (0.4–5.5)	2.0 (1.0–3.4)	2 (0.5–5.0)
1994	1.2 (0.6–2.1)	0.7 (0.0–3.8)	1.2 (0.5–2.4)	2.4 (0.8–5.5)
1995	1.5 (0.8–2.5)	0.0 (0.0–2.5)	1.8 (0.9–3.1)	0.4 (0.0–2.4)
1996	0.9 (0.4–1.8)	0.7 (0.0–3.9)	2.0 (1.1–3.4)	2.2 (0.7–5.2)
1997	1.5 (0.8–2.6)	1.4 (0.2–5.0)	1.2 (0.6–2.3)	1.3 (0.3–3.9)
1998	1.0 (0.4–2.0)	0.0 (0.0–2.5)	2.7 (1.7–4.1)	0.3 (0.0–2.2)
1999	1.4 (0.7–2.4)	2.1 (0.4–6.0)	3.0 (2.0–4.5)	2.1 (0.7–4.9)
2000	1.2 (0.6–2.2)	0.7 (0.0–3.8)	2.3 (1.3–3.6)	1.2 (0.2–3.6)
2001	1.1 (0.5–2.0)	2.6 (0.7–6.8)	2.6 (1.6–4.0)	0.7 (0.1–2.6)
2002	1.4 (0.7–2.5)	2.1 (0.4–6.1)	2.2 (1.3–3.5)	2.8 (1.1–5.8)
2003	1.6 (0.9–2.8)	1.3 (0.2–4.9)	2.4 (1.4–3.7)	1.2 (1.1–3.5)
2004	1.1 (0.5–2.1)	1.3 (0.2–4.8)	2.3 (1.4–3.5)	0.7 (0.1–2.7)
2005	0.9 (0.4–1.9)	1.3 (0.2–4.9)	1.7 (0.9–2.7)	1.3 (0.4–3.5)
2006	1.9 (1.0–3.2)	3.1 (0.9–7,9)	3.4 (2.3–4.8)	1.6 (0.4–4.0)
2007	2.1 (1.2–3.5)	0.6 (0.0–3.7)	3.3 (2.2–4.6)	2.4 (1.0–5.0)
2008	2.1 (1.2–3.5)	2.0 (0.4–6.0)	3.1 (2.1–4.4)	1.9 (0.7–4.2)
2009	1.5 (0.8–2.8)	0.8 (0.0–4.4)	2.3 (1.4–3.5)	1.7 (0.5–4.0)
2010	1.6 (0.8–2.9)	2.1 (0.4–6.3)	2 (1.2–3.1)	1.0 (0.2–2.9)
2011	2.7 (1.6–4.2)	2.2 (0.4–6.4)	2.9 (1.9–4.2)	1.5 (0.5-3.7)
APC (%) (95% CI ***p*-value**	4.3 (2.9–5.7) <0.001	*** N/A	4.0 (1.9–6.1) 0.001	0.8(-2.3–4.1) 0.60

Abbreviations: APC, annual percentage change; CI, confidence interval; IR, incidence rates. Patients of American Indian (small numbers) or unknown race/ethnicity were excluded. ***Could not be estimated.

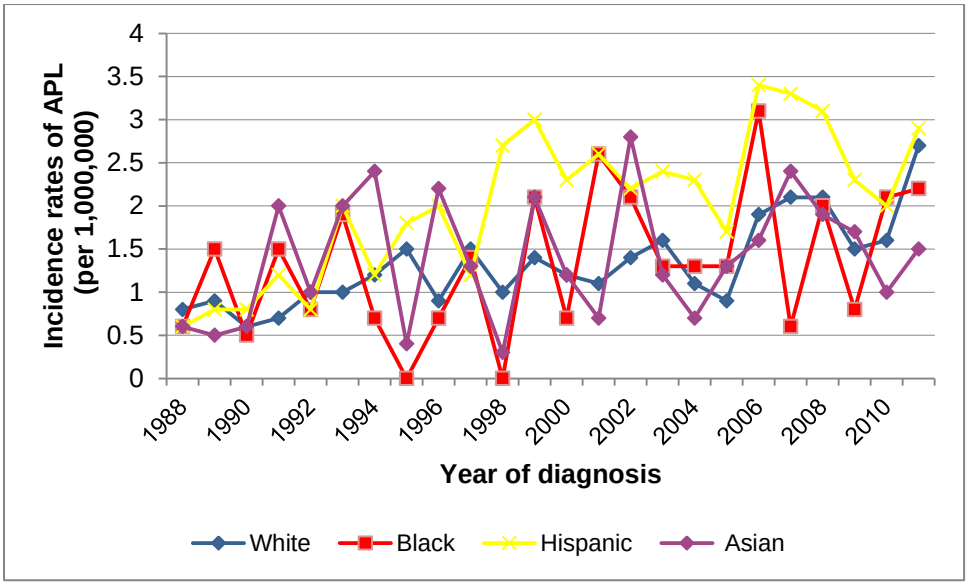

Figure 6.2: Age-adjusted incidence rates of acute promyelocytic leukaemia (per 1,000,000), by race/ethnicity, for patients aged 0–39 years, California, 1988–2011.

Chapter 7 Predictors of early death and survival among children, adolescents and young adults with acute myeloid leukaemia in California, 1988–2011: a population-based study

7.1 Preamble to research paper 3

In the background chapter and literature review, I discussed acute myeloid leukaemia as a disease that more often affects older adults, however, it can happen at any age at diagnosis, even in newborns. I have also learned that, despite improvement in treatment, supportive care and haematopoietic stem cell transplantation in the last few decades, survival from this disease is still low and acute myeloid leukaemia remains the leading cause of cancer deaths among patients ≤ 39 years.

I recognised that there was a lack of population-based studies focusing on children, adolescents, and young adults with this disease. Therefore, I aimed at investigating trends in survival and early death (i.e, death occurring within 30 days of diagnosis) among this population during 1988–2011 using data from the California Cancer Registry. I have examined the association between sociodemographic and clinical factors, including neighbourhood socioeconomic status, health insurance, race/ethnicity, hospital type, age and sex, with survival and early death. I have also provided descriptive information on treatment (chemotherapy and haematopoietic stem cell transplantation) and on patient's cause of death.

In the multivariable analyses, I presented the overall findings and also the results by age groups because of my *a priori* hypothesis that socioeconomic and demographic factors (race/ethnicity, neighbourhood socioeconomic status, treatment facility and health insurance status) would have a greater impact on older versus younger patients.

My study demonstrated that mortality among young patients with acute myeloid leukaemia remains high in California, particularly among those patients older than 9 years. My results highlighted the main factors associated with worse outcome and suggested possible strategies to improve survival from this severe malignancy.

7.2 Research paper 3

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 association 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% CI 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 centers, and black race/ethnicity. For 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 specialised cancer centres.

INTRODUCTION

Acute myeloid leukaemia (AML) is a complex and highly heterogeneous disease. Without treatment, most patients die within weeks or months of diagnosis[333]. 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[163, 334] and acute leukaemias, including AML, remain the leading cause of cancer deaths among patients aged 39 years or younger[2, 3]. 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[335, 336]. 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.[337-342]

Given the lack of population-based studies focusing on young patients with AML[10], 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%.[323] 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 center), whether the patient has undergone chemotherapy or

hematopoietic 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 HIPAA authorization.

We identified all patients aged 0 to 39 years who were diagnosed with de novo AML between January 1, 1988 and December 31, 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.[343] 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)[305]: 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 (December 31, 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.[5, 225, 226, 344, 345] 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,[255] which is based on block-level census data, and is considered an adequate surrogate to SES at the individual level.[257, 346] 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 centers (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[18, 226, 228, 325, 347, 348] 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 differs among groups for each covariate. The Kruskal-Wallis test was also used for ordinal covariates (age group, neighborhoud SES and calendar period). We used multivariable 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[267] 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 multivariable 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 multivariable 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 7.1). 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 7.1). Overall, in unadjusted analyses, early death was strongly associated with age, hospital designation, neighbourhood SES, and health insurance status (Table 7.1). In multivariable analyses in which all variables were mutually adjusted (Table 7.2), 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[349] 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 50.0% (95% CI 47.0–52.9) in 2004–2011 (Table 7.1). Based on the log-rank test, there was evidence of an association between worse survival and older age at diagnosis (Figure 7.1), 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 multivariable Cox regression analysis in which all variables were mutually adjusted (Table 7.3), 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 7.4 and 7.5), we observed that the association between the hazard of death and sociodemographic and clinical factors varied by age group. Table 7.4 presents Cox models for the factors available during 1988–2011 (all variables except health insurance status) by age group at diagnosis. Table 7.5 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 7.4). 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 7.4) and, during 1996–2011, among uninsured patients (HR = 1.78, 95% CI 1.14–2.76) (Table 7.5). 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 7.4). 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 we 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).[226, 228-230, 322, 329, 340-342, 347] 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.[230] 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[230]. 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. [230, 342] It is possible that pharmacogenetic differences between black and white patients contribute to different responses to chemotherapy.[230, 350] 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.[348]

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 of the Children's Oncology Group (patients aged 0 to 21 years),[329] but is consistent with the population-based study mentioned above[348] that found survival among Hispanics to be similar to that among white patients after adjustment for age (all ages included), and with pediatric clinical trials that showed favourable outcomes among Hispanic patients with AML.[230] These observations contrast with the worse survival observed among Hispanic children and adolescents with ALL in the US[302, 303, 328, 347] and suggest that unfavourable biological characteristics are associated with survival after ALL,[303] 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.[230]

Clinical[329] and population-based studies[348] 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 likely 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 pediatric AML differs from that of adult AML and that structural and numerical chromosome alterations have prognostic implications.[52, 233, 235] 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[52]. Additionally, somatic mutations

in selected genes such as *FLT3*, *NPM1,* and *CEBPA* are known to have prognostic clinical significance in pediatric and adult AML. Whereas double *CEBPA* and isolated *NPM1* mutations are associated with a reduced risk of relapse and better survival[234, 351] , 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.[207] Adult AML has a higher prevalence of *FLT3/ITD* mutations compared to pediatric AML (27% vs. 12%).[52] These cytogenetic and genomic differences may, in part, 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 pediatric patients.[352] We had no information on patients' clinical trial enrollment, but our observations support the results from a previous study[18] 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,[228, 353, 354] 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.[355] Although improvements in HSCT have led to a significant decrease in transplant-related morbidity and mortality in patients with AML,[355] 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 patients with AML that has a favourable prognosis (CBF AML),[356] and the use of HSCT may be limited to intermediate-risk patients who experience relapse after undergoing initial therapy.[357]

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).[358] 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,[359] 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[360] and big data infrastructure (including access to electronic medical records and linkage of cancer registry data with insurance claims information),[16] 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 [16], 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 specialised cancer centrers.

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CONFLICT OF INTEREST DISCLOSURE: The authors declare no conflict of interests

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.

Table 7.1 Patient characteristics, early death and overall survival in patients aged 0 to 39 years with acute myeloid leukaemia in California, 1988–2011

Characteristics	Total *N* (%)	Early death *N* (%)	*P*[a]	1-year OS (95% CI)	5-year OS (95% CI)	10-year OS* (95% CI)	*P*[b]
Total	3935 (100)	332 (8.4)		66.8 (65.3–68.3)	42.8 (41.2–44.4)	39.6 (38.0–41.3)	
Calendar period							
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
Age at diagnosis, years							
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					
Race/ethnicity							
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
Sex							
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
Initial care at hospitals affiliated with NCI-designated cancer centres							
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
Neighbourhood socioeconomic status (quintiles)							
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
Health insurance status (limited to patients diagnosed in 1996–2011, *N* = 2632)							
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. [a]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). [b]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.

Table 7.2 Relation of sociodemographic and clinical factors to early death in patients aged 0 to 39 years with acute myeloid leukaemia in California, 1988–2011

Characteristics	Adjusted OR1 1988–2011(95% CI)	*P*-value*	Adjusted OR2 1996–2011(95% CI)	*P*-value*	Adjusted OR3 1996–2011 (95% CI)	*P*-value*
Calendar period						
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
Sex						
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
Age at diagnosis, years						
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
Race/ethnicity						
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
Neighbourhood socioeconomic status (quintiles)						
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)	
5. Highest 20%	1 (reference)	0.0934	1 (reference)	0.4512	1 (reference)	0.4411
Initial care at hospitals affiliated with NCI-designated cancer centres						
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
Health insurance status (limited to patients diagnosed in 1996–2011, *N* = 2632)						
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 with insurance (1996–2011). *Likelihood ratio test.

Table 7.3 Relation 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

Characteristics	Adjusted HR1 1988–2011 (95% CI)	*P*-value*	Adjusted HR2 1996–2011 (95% CI)	*P*-value*	Adjusted HR3 1996–2011(95% CI)	*P*-value*
Calendar period						
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
Age at diagnosis, years						
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
Race/ethnicity						
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
Sex						
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)	0.8349
Neighbourhood socioeconomic status (quintiles)						
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)	
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
Initial care at hospitals affiliated with NCI-designated cancer centres						
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
Health insurance status (limited to patients diagnosed in 1996–2011, *N*=2632)						
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	N/A	1.27 (1.07–1.51)	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.

Table 7.4 Relation of sociodemographic and clinical factors to the hazard of death after acute myeloid leukaemia by age group, California, 1988–2011

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*
Calendar period								
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
Race/ethnicity								
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
Sex								
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
Neighbourhood socioeconomic status (quintiles)								
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
Initial care at hospitals affiliated with NCI-designated cancer centres								
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.

Table 7.5 Relation 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

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*
Calendar period								
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
Race/ethnicity								
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
Sex								
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
Neighbourhood socioeconomic status (quintiles)								
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
Initial care at hospitals affiliated with NCI-designated cancer centres								
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
Health insurance status								
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.

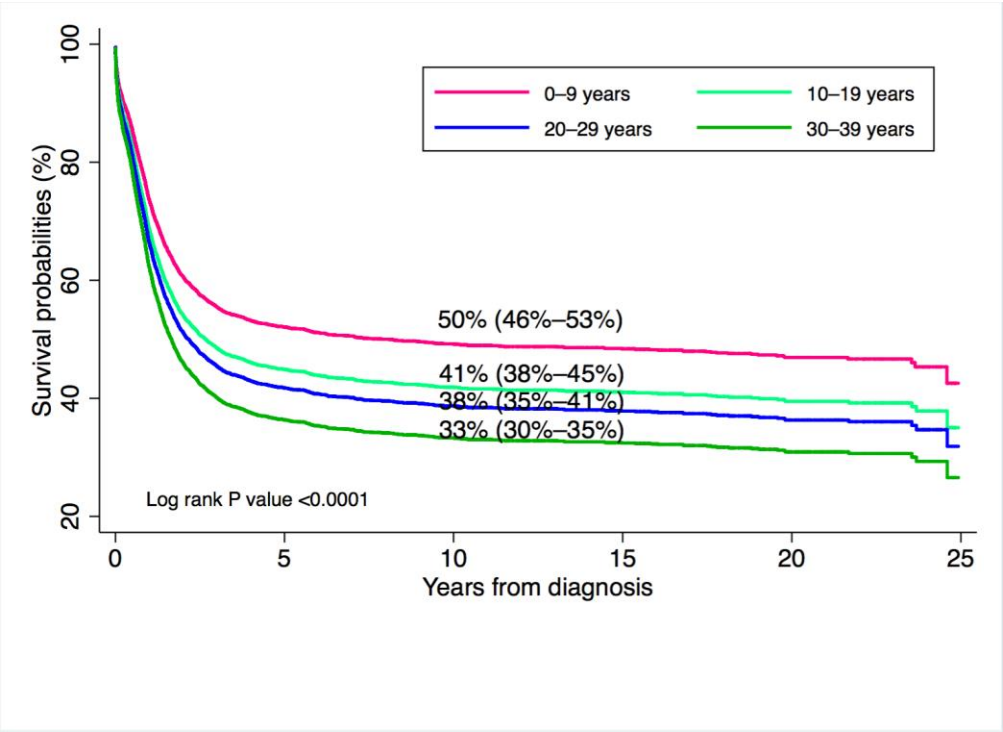

Figure 7.1 Overall survival after acute myeloid leukemia by age group at diagnosis, in California, 1988–2011 (percentages in the graph correspond to 10-year survival)

7.3 The incidence of acute myeloid leukaemia in children, adolescents and young adults in California

For acute myeloid leukaemia (AML non-APL), there is no statistical evidence of an annual increase in incidence rates since 1988 for any race (Table 7.6). The incidence rates and annual percentage change (APC) were calculated using SEER*Stat v.8.3.1 (http://seer.cancer.gov/seerstat/).

Table 7.6: Age-adjusted incidence rates (per 1,000,000) and annual percentage change of acute myeloid leukaemia, by race/ethnicity, in children aged 0–39 years, California, 1988–2011.

	White IR (95% CI)	Black IR (95% CI)	Hispanic IR (95% CI)	Asian IR (95% CI)
Total	8.5 (8.1–9.0)	8.4 (7.4–9.4)	8.6 (8.2–9.0)	9.3 (8.5–10.1)
1988	9.5 (7.7–11.7)	5.6 (2.4–11.1)	8.1 (5.9–10.9)	9.1 (5.1–14.8)
1989	8.4 (6.7–10.5)	7.2 (3.7–12.7)	8.5 (6.3–11.2)	9.1 (5.1–14.8)
1990	7.6 (6.0–9.6)	11.1 (6.3–18.1)	10.5 (8.0–13.4)	9.7 (5.8–15.4)
1991	6.5 (5.0–8.3)	14.0 (8.5–21.6)	8.1 (6.0–10.7)	12.1 (7.7–18.0)
1992	8.9 (7.1–11.0)	9.2 (5.1–15.3)	8.4 (6.3–10.9)	8.4 (5.0–13.3)
1993	7.9 (6.2–10.0)	12.3 (7.3–19.2)	8.5 (6.5–11.1)	11.3 (7.3–16.8)
1994	9.3 (7.4–11.5)	7.1 (3.5–12.8)	8.0 (6.0–10.4)	10.9 (7.0–16.2)
1995	9.8 (7.9–12.1)	4.3 (1.7–8.9)	7.4 (5.5–9.7)	5.5 (2.9–9.5)
1996	6.7 (5.1–8.7)	11.1 (6.5–17.9)	8.3 (6.3–10.6)	12.1 (8.0–17.6)
1997	8.1 (6.3–10.2)	7.3 (3.6–13.1)	10.7 (8.4–13.3)	8.54 (5.2–13.2)
1998	9.1 (7.2–11.4)	11.0 (6.4–17.7)	8.9 (6.9–11.3)	7.8 (4.7–12.3)
1999	11.3 (9.1–13.9)	9.3 (5.1–15.6)	8.2 (6.3–10.4)	10.4 (6.5–15.3)
2000	7.1 (5.4–9.2)	9.4 (5.2–15.9)	7.9 (6.1–10.1)	7.1 (4.2–11.3)
2001	8.3 (6.4–10.5)	6.8 (3.3–12.6)	9.0 (7.1–11.2)	7.7 (4.6–12.0)
2002	9.5 (7.4–11.9)	10.8 (6.2–17.6)	7.2 (5.5–9.2)	7.8 (4.8–12.1)
2003	7.0 (5.3–9.1)	7.2 (3.5–13.2)	9.7 (7.7–12.0)	8.0 (4.9–12.1)
2004	6.7 (5.0–8.9)	7.7 (3.8–13.8)	7.7 (6.0–10.0)	9.5 (6.0–14.2)
2005	8.5 (6.5–10.9)	7.3 (3.6–13.2)	8.2 (6.4–10.2)	7.6 (4.7–11.7)
2006	8.0 (6.1–10.3)	4.2 (1.5–9.1)	9.1 (7.3–11.3)	9.0 (5.8–13.2)
2007	10.4 (8.1–13.0)	4.4 (1.6–9.7)	8.5 (6.7–10.6)	9.3 (6.1–13.6)
2008	11.0 (8.7–13.7)	7.4 (3.5–13.6)	7.6 (5.9–9.6)	8.2 (5.1–12.3)
2009	8.7 (6.6–11.1)	8.6 (4.4–15.0)	9.7 (7.8–11.9)	8.4 (5.4–12.6)
2010	9.3 (7.1–11.9)	6.9 (3.1–13.2)	8.2 (6.5–10.2)	12.1 (8.3–16.9)
2011	8.1 (6.1–10.6)	8.8 (4.2–15.9)	10.0 (8.1–12.2)	9.23 (6.0–13.5)
APC (%) (95% CI)	0.4 (-0.6–1.3)	-1.5 (-3.3–0.3)	0.1 (-0.5–0.8)	-1.0 (0.1– -2.2)
***p*-value**	0.44	0.10	0.67	0.12

Abbreviations: APC, annual percentage change; CI, confidence interval; IR, incidence rates.
Patients of American Indian (small numbers) or unknown race/ethnicity were excluded.

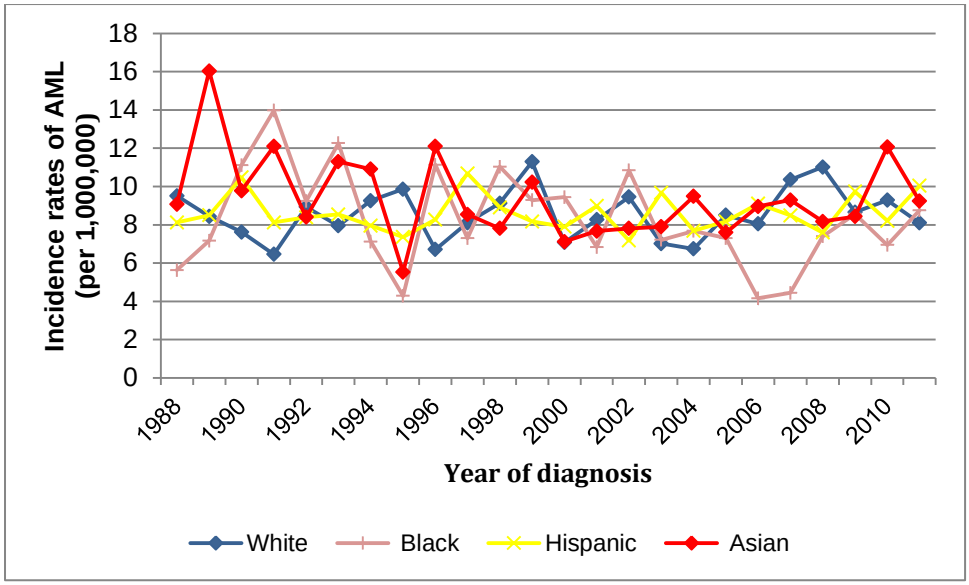

Figure 7.2: Age adjusted incidence rates of acute myeloid leukaemia (per 1,000,000), by race/ethnicity, for patients aged 0–39 years, California, 1988–2011.

Chapter 8 Discussion

"Of all the forms of inequality, injustice in health is the most shocking and inhumane"

Dr Martin Luther King, Jr.

(Speech to the Medical Committee for Human Rights, 1966)

8.1 Introduction

In the last 50 years, national and international clinical trials have allowed dramatic improvements in survival after acute leukaemia in children, adolescents and young adults. However, the treatment of some high-risk subtypes of acute lymphoblastic leukaemia and management of acute myeloid leukaemia (APL and non-APL AML) remain challenging, and acute leukaemia is currently the leading cause of cancer death among patients aged 39 years or younger in the developed world.[2, 3] Strikingly, inequalities in outcomes continue to be reported, particularly among patients from different socioeconomic, racial/ethnic and age groups.

Funded by the *Children with Cancer UK*, this thesis had, initially, the primary goal to investigate how survival among children and adolescents with the most frequent type of malignancy, acute lymphoblastic leukaemia, has varied over a long period of follow-up in California. In addition, I aimed at investigating the predictors of survival inequalities in this high-resource State of the United States.

During my literature review, I realised that the knowledge about early death and survival after acute promyelocytic leukaemia and acute myeloid leukaemia (non-

APL) is mainly based on clinical trials in the United States[10] and Europe,[186] with a lack of population-based studies for the young adult population. In 2011, Lehmann et al.[186] reported very high early death after acute promyelocytic leukaemia in a population-based study in Sweden that included 105 unselected patients aged 19 years or older, at 6.4 years median follow-up time. The authors concluded "population-based data are needed as a supplement to data from large randomised trials for information about the overall APL population". Therefore, I opted to study early death and survival after APL and non-APL AML extending the age range to young adults (20–39 years). APL is very rare under 3 years of age, its incidence increases until adulthood and remains basically constant up to 60 years, when it begins to decline.[180, 181] Conversely, non-APL AML increases sharply with age.[236] The study of survival among older adults with APL and non-APL AML is of great interest, however this was not the subject of my thesis and may be considered in my future studies. Considering these factors, I focused my thesis on the health outcomes of patients aged up to 19 years for ALL and up to 39 years for APL and non-APL AML.

The primary goals of this thesis were to evaluate trends in outcomes (survival and, when appropriate, early death) in children, adolescents and young adults with acute leukaemia in California during nearly 25 years, and to investigate the main predictors of outcomes. These overall goals were achieved by focusing on the following specific objectives:

1. To evaluate survival trends after acute lymphoblastic leukaemia in children and adolescents (0–19 years), and examine the association of survival with sociodemographic and selected clinical factors.

2. To investigate early death and survival after acute promyelocytic leukaemia among patients aged 0–39 years before and after the approval by the US FDA of all-*trans* retinoic acid (November 1995), and to evaluate the association of various sociodemographic and clinical factors with these two outcomes.

3- To evaluate survival and early death trends after acute myeloid leukaemia (excluding acute promyelocytic leukaemia) among patients aged 0–39 years, and examine the influence of sociodemographic and selected clinical factors on these outcomes.

In the next sections, I summarise the main results of my thesis providing a critical review of these findings (section 8.2), and discuss the main contributions of my work to the field of paediatric and young adult haematology, as well as the implications for policy makers and researchers (section 8.3). Next, I consider the relationship between socioeconomic status, race/ethnicity and survival, and discuss an alternative analytical approach apart from those I have chosen for my studies (section 8.4). Finally, I consider the limitations of my studies (section 8.5), discuss my future research plans (section 8.6) and give the concluding remarks (section 8.7).

8.2 Overall findings of the thesis

The **literature review (Chapter 3**) highlighted the need for further studies aimed at investigating whether the survival inequalities by age (children, adolescents and young adults) observed among patients with acute leukaemia have decreased over time.

In addition, it raised a question about the extent to which paediatric protocols have been adopted by adult haematologists to treat older patients (15–39 years) with acute lymphoblastic leukaemia.

This review also emphasised the value of more population-based studies to learn whether the improvement in survival and trends in early death after acute myeloid leukaemia observed in clinical trials can be generalised to the entire population in the United States and elsewhere.

Finally, reports of inequalities in survival and early death among different racial/ethnic and socioeconomic groups within and between countries revealed the need for further studies to identify the main predictors of outcomes.

Research paper 1 (Chapter 5) revealed remarkable improvement in survival in children and adolescents with acute lymphoblastic leukaemia in California during 1988–2011. Similar to previous studies, infants (< 1 year) and older children (10–19 years) fared worse than children aged 1–9 years. However, even after adjustment for other covariates, socioeconomic and racial/ethnic survival inequalities existed and persisted over time. Non-white patients had worse survival than white patients, with the most striking differences observed among blacks and Hispanics. In addition, patients living in the lowest socioeconomic neighbourhoods had lower survival than those living in the highest socioeconomic neighbourhoods.

Moreover, my study revealed the proportion of patients who developed secondary neoplasm (1.8%) after treatment of childhood acute lymphoblastic leukaemia during a long period of follow-up (nearly 25 years). This finding is consistent with previous reports in the literature which showed that the incidence of secondary malignancy varied from less than 1% to 10% in this population.[299, 361-367] The variability of these findings has been attributed to differences in therapeutic

protocols, accuracy in the reports and completeness of follow-up.[298] The majority of these reports come from clinical trials in developed countries, emphasizing the importance of also collecting this information at the population level, especially in low- and middle-income countries. This will require improvement in cancer registration in these countries.

In this study, access to care measured through health insurance status and treatment facility (whether a paediatric cancer centre or not) did not have a significant association with survival. This may be explained by the fact that all children and adolescents with cancer in California are entitled to health coverage through the California Children's Service and they tend to be referred to hospitals where they can get treatment, even if they are undocumented immigrants.

The majority of patients (~70%) with ALL received initial care at specialised paediatric cancer centres where they are usually enrolled in COG clinical trials and receive standardised therapeutic protocols. I did not find an association between survival and treatment facility (whether it was a cancer centre or not), but this may be because data available in the California Cancer Registry refer to the treatment facility where the patient received initial care. Therefore, it is possible that some patients diagnosed at a non-specialised cancer centre may later have been transferred to a specialised hospital for further investigation or treatment.

These findings suggest that the racial/ethnic and socioeconomic inequalities observed in my study cannot be solely explained by access to care. In fact, in the UK, where all children have access to standard treatment though the National Health Service (NHS), socioeconomic inequalities have also been reported. In a national population-based study,[120] inequalities were worse during the maintenance phase of therapy when most treatment is given at home (combination therapy), with a monthly

outpatient visit. This suggests that even in developed nations with universal health systems, adherence to treatment can be a major issue.

Adherence to treatment may have contributed to the survival inequalities observed in my study, but there were no data on this to allow an investigation. In the US, one study[309] demonstrated that when adherence to oral 6-mercaptopurine (a medication that should be taken daily during the two-year maintenance phase) was below 90% in children and adolescents aged 1–19 years with ALL, the risk of relapse was increased 3-fold. Additionally, 31% of relapses were attributable to non-adherence. Interestingly, the authors found that a higher proportion of non-adherers were black and Asian patients compared to non-Hispanic white patients. Among blacks and Asians, race-specific sociodemographic factors such as low maternal education, single-parent/multiple-children families and low-income families without mothers as full-time caregivers, were associated with low adherence to treatment. Another study[368] revealed that Hispanic patients also had lower compliance to oral 6-mercaptopurine regimens and a higher risk of relapse than white patients. These studies support previous evidence that race/ethnicity and SES in the US are intimately related.[369, 370]

Undocumented immigrants

California has more than 10 million immigrants, corresponding to about 27% of the State population, about twice the US national proportion. Approximately 47% of foreign-born residents in California are naturalized US citizens, 26% have a green card or another type of visa, and about 26% are undocumented. The majority of immigrants are from Latin America (53%), but recently more immigrants have come from Asia (37%).[371] California immigrants are more likely than US-born families to

live in poverty (below 200% of the federal poverty level threshold, Table 8.1). Factors such as lower education, lack of awareness about the seriousness of acute leukaemia, fear of legal problems among undocumented immigrants and financial problems may all lead parents to delay taking their children to the doctor. It is not uncommon for patients to miss hospital appointments during the long and complex treatment of ALL, for a variety of social, cultural and economic reasons. All these factors, together with disease biology, may have contributed to the survival inequalities observed in this vulnerable, disadvantaged population of California. The data used on my thesis have no information on the legal status of immigrants.

Table 8.1 Children under 18 years living in low-income families (below 200% of poverty level threshold) by family nativity in California. Source: Adapted from National Kids Count (http://datacenter.kidscount.org/data).†

Children in Immigrant Families	Data Type	2010	2011	2012	2013	2014
Children in immigrant families	Number	2.502,000	2,513,000	2,506,000	2.427,000	2,376,000
	Percent	56%	57%	56%	56%	55%
Children in US-born families	Number	1,732,000	1.824,000	1,825,000	1,844,000	1,722,000
	Percent	37%	39%	39%	39%	38%

Research paper 2 (Chapter 6) showed substantial improvement in early death (30-day mortality) and survival after acute promyelocytic leukaemia in patients aged 0–39 years after the introduction of all-*trans* retinoic acid (1996 onwards, the ATRA era) compared with patients treated in the pre-ATRA era (1988–1995) in California. However, compared with levels reported in clinical trials (3%–8%), early death remained high even in the most recent calendar period (14% in 2004–2011).

† Based on the Population the US Census Bureau, Census 2000 Supplementary Survey, 2001 Supplementary Survey, 2002 through 2014 American Community Survey.

The majority of patients who had early death died within the first week of diagnosis, and there was no evidence of improvement in 7-day mortality over time. When patients who died within 7 days of diagnosis were excluded from the analysis, early death results (the proportion who died within 8–30 days of diagnosis) were similar to those reported in clinical trials. Likewise, when patients who died within 30 days were excluded from the analysis, survival after acute promyelocytic leukaemia was close to that described in trials. These findings, of similar outcomes only when subgroups were excluded, highlight that bias in survival estimates (usually overestimation) may occur when evaluating selected patients, because high-risk and very ill patients are not usually enrolled in clinical trials. Importantly, this study showed that, at the population-base level, many young patients in California still die from APL, a highly curable disease. The main predictors of worse survival and early death in this study were Hispanic and black race/ethnicity and lack of health insurance (for patients diagnosed during 1996–2011). Delay in diagnosis and treatment delays of more than 2 days after diagnosis of APL may be the main reason 7-day and 30-day mortality were persistently high in California during the study period.

Lack of insurance for young adults and undocumented immigrants in California

California has about 2.7 million undocumented immigrants, mostly from Latin America. Of these, approximately 1.5 million are uninsured.[372] Some undocumented immigrants who have insurance (approximately 30%–40%) may be covered by their employers or buy their insurance on the individual market. The remaining 60% to 70% of young adult documented immigrants who are uninsured, have very few health care options. County governments can choose whether to offer health

insurance for this population through indigent programs. Of relevance, it has been estimated that about 875,000 undocumented immigrants live in counties that do not offer health care through the indigent care program.[372] Currently, California counties that offer health care for the uninsured immigrants are: San Francisco, San Mateo, Santa Cruz, Alameda, Santa Clara, Contra Costa, Fresno, Kern, Ventura, Los Angeles and Riverside. The safety net providers (mostly community clinics and emergency departments) provide care for patients regardless their immigration status, however, they do not provide comprehensive health care.

According to a new survey, about 68% of California adults who were previously uninsured, have obtained health insurance since the implementation of the national Affordable Care Act (ACA). Eligible Hispanics and whites gained coverage at similar rates. However, despite the health insurance expansion that has occurred after the implementation of the ACA in 2014, undocumented immigrants were excluded from enrolment. It is estimated that Hispanics still comprise 41% of remaining uninsured individuals (Figure 8.1).

In June 2015, the California Senate approved a bill that will allow many undocumented immigrants to enrol in special healthcare programs aimed to offering the same benefits as Medi-Cal (http://www.latimes.com/local/political). This measure will allow approximately 240,000 children to enroll to Medi-Cal and some low-income adults to enrol to a health plan that provide similar services than Medi-Cal. If this measure is effectively implemented, it may significantly improve access to care for undocumented immigrants with several diseases, including cancer. Consequently, it is expected that the increase in health insurance coverage through the full implementation of the Affordable Car Act will improve access to care for young adults with cancer and, hopefully, decrease mortality from this disease.

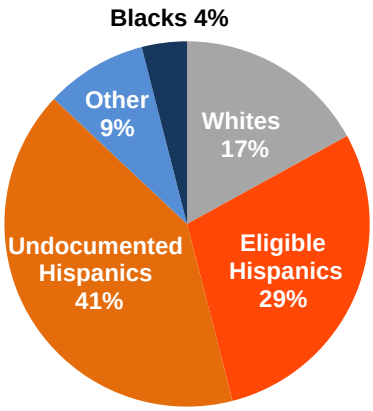

Figure 8.1: Demographics of California's remaining uninsured population by race/ethnicity. **"**Eligible" refers to individuals who are eligible for enrolment in the Affordable Care Act (ACA) based on their immigration status (citizen, permanent resident, or legally present immigrant). "Undocumented" are those individuals who are not eligible to apply for ACA due to their immigration status. Adapted from Wave 3 of the Kaiser Family Foundation California Longitudinal Panel Survey (February 18–May 13, 2015) (www.kff.org).

Research paper 3 (Chapter 7) demonstrated that despite survival improvements after acute myeloid leukaemia (non-APL) in children, adolescents and young adults (0–39 years) in the last 25 years, 5-year survival has remained at only 50% or less in the modern era of treatment (2004–2011). There was a trend towards a decline in early death over the study period. The main factors associated with lower survival were older age (> 9 years), treatment at non-specialised cancer centres, black race/ethnicity and lack of health insurance (for patients diagnosed during 1996–2011). My findings also suggested that the impact of these factors on survival varied by age group, with stronger associations among older patients (10–39 years).

This study on non-APL AML has revealed an association between treatment at specialised cancer centres and survival, which was not found in the APL study.

Whereas APL has an established effective treatment with ATRA and/or arsenic combined with chemotherapy, non-APL AML is a very heterogeneous disease and more effective and less toxic drugs are, hopefully, still to be discovered. Haematopoietic stem cell transplantation may be a crucial treatment option in many cases. Because of the complexity of this treatment, it requires a multidisciplinary team and a specialised cancer centre. The complexity of non-APL AML treatment may, in part, explain the worse survival among patients who were not treated in these centres.

Similarly to the ALL and APL studies, black patients with non-APL AML fared worse than whites. In addition to the influence of sociodemographic and economic factors on survival inequalities previously discussed, lower availability of matched family bone marrow donors may be a possible explanation for the survival gap between black and white patients, as reported by a number of studies.[373, 374]

8.3 Main contributions of the thesis and implications for policy makers and researchers

The work of this thesis provides important information for clinicians, researchers and policy makers who aim to improve the long-term survival of children, adolescents and young adults with acute leukaemia. The main contributions of my thesis are highlighted below.

The results of my literature review and research paper 1 (Chapter 5) show persistent racial/ethnic and socioeconomic survival inequalities for patients with acute lymphoblastic leukaemia. This calls for actions and programmes to decrease the survival gap between these subgroups of patients. This may include, but is not limited to, prompt access to adequate therapy, better education of parents and

patients about the severity and prognosis of the disease, comprehensive psychosocial support, and monitoring of treatment compliance. Economic support for parents who need to stop working to care for their children may be warranted.

Moreover, reports of significantly worse survival among adolescents and young adults with acute lymphoblastic leukaemia should be further investigated. Have adolescents and young adults with ALL been treated by adult oncologists adhering to paediatric protocols, as studies have shown that they are more effective and improve survival? A pilot population-based study recently performed in Northern California showed that, as recently as 2014, fewer than 25% of adolescents and young adults with ALL were treated with paediatric protocols at adult centres. I am a co-author of a paper titled "Adoption of Pediatric-Inspired Acute Lymphoblastic Leukemia Regimens by Adult Oncologists Treating Adolescents and Young Adults: A Population-Based Study", which was recently submitted to a peer-reviewed journal and the abstract was accepted for poster presentation at the 2016 American Society of Clinical Oncology (ASCO) annual meeting.

The findings of my second study on early death after acute promyelocytic leukaemia showed that, at the population-based level, early death has decreased, but is still high in the more recent era of treatment. My results also revealed worse outcomes for patients of Hispanic and black race/ethnicity and those without health insurance, pointing to an unmet need to address inequalities among vulnerable patients. This may include wider insurance coverage and access to optimal care. Moreover, health care providers should be educated to recognise acute promyelocytic leukaemia as an emergency that needs immediate initiation of therapy with ATRA as soon as this disease is suspected. Of great relevance, hospital

administrators and pharmacists should make sure that ATRA is available for prompt use when requested by physicians.

The results from my third study demonstrated that survival from acute myeloid leukaemia, excluding acute promyelocytic leukaemia, remains low in the most recent era of treatment. In this high-resource country, young acute myeloid leukaemia patients with health insurance (private or public) and those who received initial treatment at hospitals affiliated with NCI-designated cancer centres had better survival than those without health insurance or treated at non-specialised centres. These results support the increasing evidence that young patients with acute myeloid leukaemia have better outcomes when treated in academic, tertiary or specialised centres than when they receive treatment at community hospitals.[18, 310, 375, 376] This may be explained, in part, by the way university hospitals and specialised cancer centres rely on a multidisciplinary team comprised of board-certified paediatric haematologists/oncologists, paediatric oncology nurses, radiologists, surgeons pathologists as well as paediatric subspecialists.[375] This approach also includes comprehensive psychosocial support, which is vital due to the heavy burden caused by this disease to patients and their families.

Furthermore, my findings emphasise the need for further genotypic and phenotypic research studies aimed at identifying patients who respond to targeted therapies. Risk-adapted therapy (or precision medicine) is expected to lead to more effective and less toxic treatment resulting in better survival than that currently achieved with conventional chemotherapy.[377]

The majority of population-based cancer registries worldwide do not provide data on various important variables such as leukaemia immunophenotype (e.g., B- or T-cell ALL), race/ethnicity (particularly on Hispanic and Asian patients),

socioeconomic status, health insurance status, cause of death, type of treatment facility at diagnosis, secondary tumours, and treatment. In this thesis, I used high-quality data from one of the world's largest population-based cancer registries, which has all these variables, except detailed information on treatment. Therefore, when I investigated survival and early death after leukaemia, I could simultaneously adjust for many variables that are recognised to influence outcome (section 4.4). The racial and ethnic diversity of the Californian population, along with the long period of observation, allowed for comparison of outcomes between different racial/ethnic groups of patients. This is especially relevant for acute leukaemia due to a higher incidence and often worse prognosis of this disease among Hispanics. Also, data from clinical trials are limited by the unequal participation of patients by race/ethnicity. Thus, differences in survival observed in clinical trials may be influenced by inadequate representation of some patient subgroups.[114, 155]

Moreover, in contrast with most cancer registries worldwide, the California Cancer Registry provides information on full dates (day, month and year) of birth, diagnosis and last known vital status, with nearly complete data. Therefore, it was possible to estimate the specific time points when death occurred within the first month after diagnosis. This enabled me to present data on 7-day mortality for acute promyelocytic leukaemia and showed that there was no improvement over time, identifying an area for improvement.

Because of the high-quality data available in the California Cancer Registry, the large sample sizes I used, and long-term of observations in my studies, it is reasonable to assume that my findings are generalizable to the rest of the US population and, probably, to other nations. However, because different countries

have diverse racial/ethnic distributions and different healthcare systems, some of the relationships I found may differ in different countries.

In a very recent national large population-based study[378] (not shown in this thesis) in which I have collaborated, we investigated survival of children, adolescents and young adults (0–39 years) with ALL, AML and Hodgkin lymphoma (HL) by age and race/ethnicity during almost four decades (1975–2012) in the US. Using SEER data, we found that survival improved significantly for ALL, AML and HL. Nonetheless, survival inequalities persisted between white and non-white patients, and between children and adolescents and young adults. This recent work has shown that same associations found in my thesis also persisted in a larger study and for another disease (HL) supporting the generalizability of my thesis work. The correspondent paper titled “Racial disparities in the survival of American children, adolescents and young adults with acute lymphoblastic leukemia, acute myelogenous leukemia and Hodgkin lymphoma” was accepted for publication in *Cancer* in April 2016 and is currently in press.

In summary, my main messages for policy makers are that substantial survival inequalities persist among patients with acute leukaemia in California leading to a considerable number of probably preventable deaths among children, adolescents and young adults. My, and various other studies, cited in this thesis provide compelling evidence that treatment, treatment adherence, sociodemographic and economic factors largely contribute to the survival differences observed among vulnerable patients. Therefore, priorities should be set and actions taken. Improving health insurance coverage for vulnerable patients – those living in low SES neighbourhoods, of black and Hispanic race/ethnicity, and undocumented immigrants – are likely to improve access to care and outcomes. However, the

quality of care provided for these patients is of extreme relevance because leukaemia is a complex disease that needs a multidisciplinary and highly skilled team of health professionals to manage potential fatal treatment complications, such as sepsis and hemorrhage. Thus, it is advisable that leukaemia patients receive treatment at specialised cancer centres with outstanding supportive care.

Additionally, all effort should be made to improve enrolment of adolescents and young adults in clinical trials, which have long been considered a “gold standard” for treatment of leukaemia and other malignancies. Low enrolment in clinical trials may partially explain the lower survival among adolescents and young adults compared with children with acute leukaemia. Also, the barriers that prevent adult haematologists from treating adolescents and young adults with acute lymphoblastic leukaemia following more effective paediatric regimens should be urgently investigated, so strategies to improve adherence to paediatric protocols can be implemented, and would likely save the lives of many young patients.

Finally, continuous surveillance is warranted to examine whether survival improvements occur in the modern era of treatment (precision medicine) and after the implementation of the Affordable Care Act, which is likely to increase insurance coverage among less privileged young adults and facilitate access to costly cancer treatment.[228] The expectation that better access to care will lead to better health outcomes is based on the assumption that coverage under the Affordable Care Act will be comparable to private insurance or Medicare. The costs of cancer care are growing faster than various other areas of medicine.[379] Medi-Cal expenditures increased from approximately 3 billion in 2011 to more than 6 billion dollars in 2014.[244] Yet, a recent study[244] using CCR data showed that patients with cancer who

had Medi-Cal or Medi-Cal dual eligibility did not have better outcomes than uninsured patients.

This is concerning and emphasises the need for close assessment of the equality of care provided by hospitals and physicians, and monitoring of health outcomes among patients covered by Medi-Cal. In this regard, it is crucial to link the data obtained by the California Cancer Registry to clinical information and insurance claims data. A press released on 18 February 2016 highlights the results of my third study on AML and emphasize some of the recommendations mentioned above. A copy in PDF of the press release is presented in Appendix 7.

8.4 Further discussions on investigating the relationship between socioeconomic, race/ethnicity and survival

In my studies, I found dramatic survival inequalities by race/ethnicity, with survival disadvantage for blacks (also called African Americans) in all three studies. This corroborates earlier reports which have shown that, in the US, blacks have higher mortality rates than whites in almost all ages and for all major diseases, including cancer.[370] Compared with whites, survival was also substantially lower among Hispanics with ALL and APL, but not among Hispanics with AML.

Acute leukaemia outcomes also differed substantially by neighbourhoods SES. For ALL and AML, survival and early death, respectively, were worse for patients living in the lower SES neighbourhoods compared to those living in the higher neighbourhoods. These racial/ethnic and SES survival and early death differences persisted even after adjustment for all variables in the multivariate Cox models including age, sex, health insurance status and treatment facility. All these

variables were considered because of *a priori* hypothesized or previously observed associations with early death or survival.[18, 226, 228, 324, 346, 347]

In the United States, it has been well recognized that race is closely related to SES and these two factors are related to survival from cancer and other diseases.[370, 380, 381] In my studies, I controlled for race/ethnicity and SES in the same multivariate model and observed that the survival differences between patients of different race/ethnicity and neighbourhoods SES persisted over time.

Figure 8.2 is a causal diagram showing the possible relationships between the explanatory variables used in my models, and survival. This suggests that SES is on the causal pathway between race/ethnicity and survival. Similarly, health insurance status and treatment facility are also on the causal pathway between race/ethnicity and survival. By including these mediator variables in the multivariable models, the adjusted estimated association between race/ethnicity and survival may be considered an indirect effect of race/ethnicity on survival. Age, sex and race/ethnicity are assumed to be confounders of the associations between SES and survival, and between health insurance status and treatment facility and survival.

The fact that I found an association between race/ethnicity and survival after adjustment for the other variables mentioned above suggests that the effect of race/ethnicity on survival is not only due to SES, health insurance status and treatment facility. There is therefore evidence that other factors related to race/ethnicity contributed to the survival inequalities. One possibility is disease biology, which was discussed in chapters 3 and 5–7 of this thesis. However, biology does not fully explain all survival differences between young patients of different race/ethnicity. Differences in quality of care provided to patients with leukaemia are likely to explain part of the survival gap.

Similarly, the associations I found between SES and survival after controlling for health insurance status and treatment facility (variables that are on the causal pathway between SES and survival), suggests that SES is not totally mediated through health insurance and treatment centre.

Several researchers have argued that race/ethnicity is a determinant of social class.[370, 382] However, differences in health outcomes cannot be solely explained by socioeconomic variables such as income, education, etc., because these factors do not fully explain causality.[381] When race/ethnicity and SES are included together in a multivariate model, it may result in an "over-adjustment" and the effect of race/ethnicity or SES, respectively, on survival can be, in fact, underestimated.

An alternative approach to the multivariate models I used in my studies would be to perform a formal mediation analysis[383, 384] which takes into account that SES, health insurance status and treatment facility are on the causal pathway between race/ethnicity and survival. The mediation analysis could disentangle the direct effects of race/ethnicity on survival from those that are mediated via SES, health insurance status and treatment facility. Similarly such analysis could disentangle the direct effects of SES on survival from those mediated via health insurance status and treatment facility.

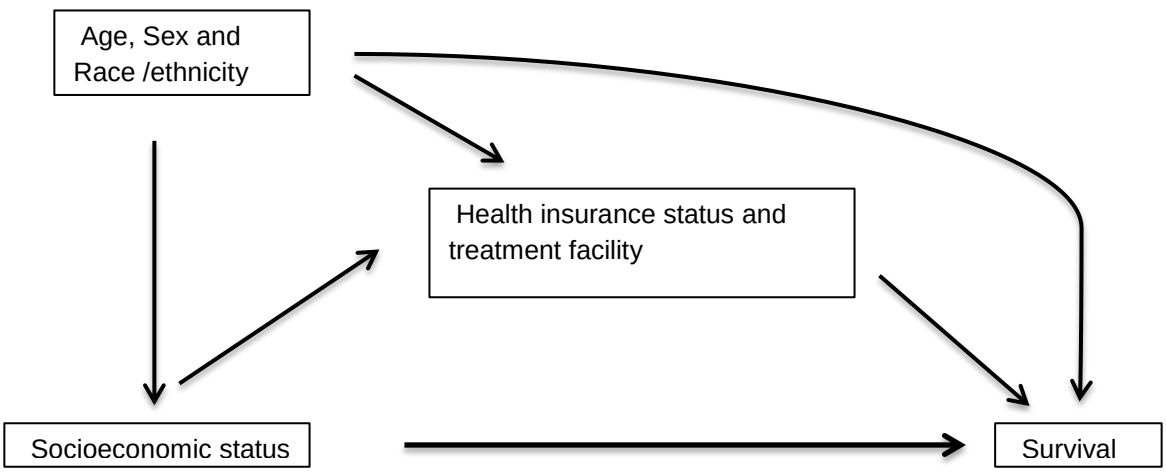

Figure 8.2: Causal diagram showing measured confounders of the exposure, mediators and outcome.

8.5 Limitations

8.5.1 Limitations of the data

The data used for the investigations presented in this thesis have a few limitations, which are mostly due to the lack of clinical data associated with the prognosis of acute leukaemia and detailed information on treatment. These data are not routinely collected by population-based cancer registries, thus it was not possible to control for these factors in the analyses. The relevant variables not available are described below. Figure 8.3 illustrates the strengths and weaknesses of cancer registry data, such as the California Cancer Registry.

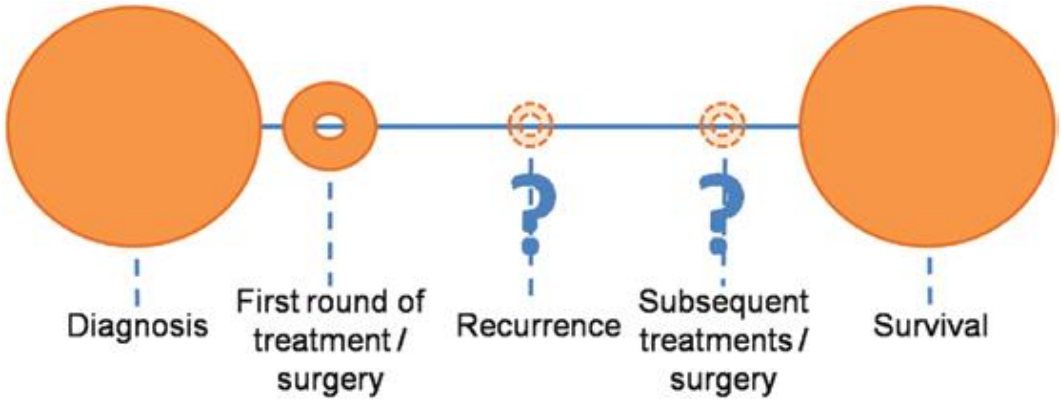

Figure 8.3: Population-based cancer registries data strengths and weaknesses. Adapted from California HealthCare Foundation and Hiatt et al., J Natl Cancer Inst 2015.[385] Cancer registries capture a wealth of information on diagnosis and survival, and some information on the first round of treatment, but nothing related to recurrence or to subsequent surgery or other treatments.

Information on **relapse** is relevant because patients who relapse after complete treatment for acute leukaemia are known to have a very poor prognosis. Therefore, the occurrence of relapse and time to relapse after chemotherapy or haematopoietic stem cell transplantation is highly predictive of outcome and is commonly used to guide further treatment approaches. Data on relapse demands

repetitive active follow-up of a large number of patients, which is challenging for population-based cancer registries.[109]

I was able to obtain descriptive information on initial treatment (chemotherapy, radiation and/or haematopoietic transplantation). However, there was no information available on the **therapeutic protocols** used, and no detailed data on transplant or subsequent treatments. In addition, data on **treatment compliance** are especially relevant for acute lymphoblastic leukaemia due to the requirement of long-term use of oral drugs (e.g., 6 mercaptopurine), but this information is not available in population-based cancer registries.

The cancer registry also lacks more detailed **clinical data**, such as white blood cell count at diagnosis, initial platelet count, cytogenetic or molecular characteristics, involvement of central nervous system disease, or minimal residual disease assessment, all factors that have been considered associated with outcome.[175, 201] Consequently, information on **group risk stratification,** which is important to guide personalised therapy, was not available.

Likewise, there was no information on **performance status,** which is highly predictive of outcome, mainly for acute myeloid leukaemia.[226, 287] However, lacking this measure in this young cohort of patients likely impacts the findings less than the analyses of older patients, as, in general, young patients are healthier, have better performance status (0–II) and fewer secondary malignancies compared with older patients.

Table 8.2 compares the type of information that can be obtained from population-based cancer registries with that which can be obtained through health insurance claims and health system electronic medical records. Clearly, the linkage of these data can improve our understanding of the disease as well as provide

information on the quality of care provided to patients, eventually improving treatment outcomes.

Table 8.2: Patient information available in each data source. Adapted from Hiatt et al., *J Natl Cancer Inst 2015* [385]

Data	Population-based cancer registries	Insurance claims data	Electronic medical records
Patient identifiers	✓	✓	✓
Patient address	✓	NA	✓
Patient demographics	✓	✓	✓
Clinical history and comorbidities	NA	✓	✓
Tumour characteristics	✓	NA	✓
Treatment data	✓ *	✓	✓
Patient reported data	NA	NA	✓ *
Post-acute care treatment	NA	✓	✓
Patient vital status	✓	NA	✓
Provider identifiers	✓	✓	✓
* = Incomplete data; NA = data not available in the data source			

Other data limitations

Potential misclassification of race/ethnicity obtained by the CCR, may have influenced the association I found in my studies between race/ethnicity and survival and/or early death. However, previous studies using cancer registry data (including California data), revealed that this variable is of very high quality for self-reported race/ethnicity for white and black patients and of moderate quality for Hispanic and Asian patients.[254, 386]

Another limitation in my studies was the lack of individual-level measures of SES to examine along with the measure of neighbourhood SES available in the CCR. Therefore, some cultural or deprivation factors associated with survival may not have been entirely captured by the neighbourhood SES variable I have used. Nonetheless, studies have shown that individual-level and census-based measures of SES are closely associated with outcomes,[306] and census-based measures of

SES may, in fact, uncover risk factors and inequalities in outcome not revealed by individual-level measures of SES.[387, 388]

8.5.2 Limitations of the analysis

In the analyses presented in this thesis, age was categorised into four (ALL) or five (APL and AML) groups. This was based on clinical knowledge and previous reports showing survival differences by age.[226] Presenting hazard ratios for categories of age allows for an easy interpretation of the estimates with age categories. However, I also recognise that information is lost when a continuous variable is categorised. Further analyses could also consider models in which age is treated as a continuous variable. In these models age could be modelled as a linear term, and in this case the hazard ratio for age would be that associated with a 1-year increase in age. It is likely that the association with age and survival could be non-linear however. Therefore, non-linear forms for age could be considered, for example using splines. The hazard ratios for age would then be best displayed graphically.

As discussed in section 8.4, a formal mediation analysis[383, 384] could be performed in order to avoid "over-adjustment" with variables that lie on the causal pathway between the explanatory variables (SES and race/ethnicity) and survival.

8.6 Areas of further research

The work presented in this thesis has suggested a number of important areas for further research aimed at improving survival of children, adolescents and young adults with acute leukaemia and other type of cancers. In this section I give background an overview of two planned specific projects I will be leading.

8.6.1 Evaluating the burden of childhood and young adult cancer in low- and middle-income countries

In my literature review, it became clear that, in order to improve the poorer survival after childhood and young adult leukaemia, as well as other types of cancer, it is critical to quantify the incidence and survival of this disease in the population, and also investigate factors associated with both incidence and survival. The work of my thesis focused on a developed country, and I am now interested in performing similar investigations in low- and middle-income countries. A future study will aim at examining the childhood cancer incidence and survival in Latin America from 1990 onwards.

Childhood cancer is a rare disease accounting for less than 2% of the global cancer burden. Yet, every year more than 160,000 children are diagnosed with cancer.[35] Missed or late diagnosis, unavailability of treatment and treatment abandonment are the main problems affecting children with cancer in low- and middle-income countries.[389] Children and adolescents living in poor-resource countries are exposed to different environmental, biological and socioeconomic conditions compared to those children living in high-resource countries. Therefore, children in Latin America may have a different incidence, type, presentation, and prognosis of cancer than children in developed countries. To decrease mortality and morbidity of children with cancer, it is essential to understand the extent to which this disease affects the population of interest, as well as age-specific cancer incidence and survival patterns. Eventually, priorities can be set with the aim of creating regional and national cancer control plans.

The main goal of this future project is to generate and provide useful information on the burden of childhood cancer in Latin America, by producing an

overview of cancer incidence in the young population. A secondary aim is to identify cancer registries that collect patients' follow-up information in order to conduct a study of childhood cancer survival, depending on the data availability and quality.

This population-based study will build on the results generated by the International Incidence of Childhood Cancer monograph, volume 3 (IICC-3, http://iicc.iarc.fr/). Around 50 populations aged 0–19 years might be available for these analyses. If required, other data sources will also be considered, in order to possibly extend the age range up to 39 years, such as the database of the *Cancer Incidence in Five Continents* (http://ci5.iarc.fr/Default.aspx) and the publication *Cancer in Central and South America*, which is close to finalisation in the beginning of 2016.

8.6.2 The association of the TP53 R337H mutation with cancer predisposition in southern Brazil

As previously discussed, genetic and molecular information can help to understand the aetiology of cancer and guide risk-stratified therapies. Previous studies have demonstrated significant correlation between patient genotype and tumour phenotype. For example, patients with inherited TP53 mutations and the classic Li-Fraumeni syndrome have a higher incidence of leukaemia, adrenocortical tumours, rhabdomyosarcoma, osteosarcoma, and central nervous system tumours than those without this syndrome. In these individuals, cancer tends to develop earlier in life.[390-393] These findings have significant implication for genetic counselling as well as clinical management (e.g., annual abdominal ultrasound for children with TP53 mutation).[390, 394, 395]

A recent study evaluated the involvement of germline predisposition mutations in paediatric tumours and revealed that 8.5% of these patients had pathogenic (or possibly pathogenic) mutations. The TP53 mutation was one of the most frequent cancer predisposing mutations in these children. In addition, the study revealed that among patients with available data on family history, only 40% had a positive family cancer history.[395]

In the South of Brazil, an inherited mutation – the TP53 R337H – has been associated with a higher incidence of adrenocortical tumour and choroid plexus in children, but not with other malignancies that characterise the classic Li Fraumeni syndrome.[394] Preliminary analysis suggests that patients with the R337H mutation also have a predisposition to other cancer types, such as breast and gastrointestinal cancers.

The main aim of this project will be to investigate the family history of children with adrenocortical tumour and a germline TP53 mutation using the public TP53 database created by the International Agency of Research on Cancer (IARC, http://www.iarc.fr/p53). My collaborators and I will compare the findings of this study with the results from a Brazilian institution. Our hypothesis is that the family history of cancer of individuals carrying low-penetrance mutations such as the R337H, is different from that of individuals with DNA binding domain TP53 mutations. The results of this study may guide genetic counselling of families of children with adrenocortical tumour and TP53 mutations.

8.7 Conclusions

My three studies revealed that outcomes after acute lymphoblastic and myeloid leukaemia have substantially improved over time in California. However, long-term

survival after acute myeloid leukaemia is still low for all ages, especially for adolescent and young adults.

Additionally, despite improvement in outcomes, I found that inequalities in early death and survival are significant and have persisted in all eras of treatment. In particular, worse outcomes were observed in disadvantaged populations, such as patients of black and Hispanic race/ethnicity, uninsured patients, and those who live in lower socioeconomic neighbourhoods. These highlight the unmet need of addressing non-biologic factors that are strongly associated with early death and survival after acute leukaemia.

Furthermore, with the conclusion of human genomic sequencing and the approval by the US Food and Drug Administration of many drugs directed to specific molecular targets, we have entered the era of precision medicine. This means that, in order to achieve better results for cancer treatments, clinicians need to understand the importance of treating subgroups of patients based on molecular signatures. Continued research to measure outcomes and adverse effects of new therapy is crucial.

The new “Cancer MoonShot 2020” Initiative launched by President Barack Obama in January 2016 and led by Vice-president Joe Biden, aims “to double the rate of progress and make a decade’s worth of advances in five years" (http://www.cancermoonshot2020.org/). This initiative has brought much enthusiasm and optimism to the medical and research communities. In March 2016, it was announced the creation of a ‘National Pediatrics Consortium’, which promises to bring “combined immunotherapy as the next-generation standard of care to children diagnosed with cancer”. This Consortium has the leadership of the Phoenix Children’s Hospital and nine other partners, including the Children’s Hospital of

Orange County in California. The focus will be to use whole genomic and proteomic analysis to generate comprehensive molecular cancer diagnosis and real-time data sharing.

While national and international collaborative trials will continue to play a key role in the development of new therapeutic approaches for all age groups with acute leukaemia, a special focus should be on adolescents and young adults who continue to have inferior long-term survival compared with children.

Finally, my research highlights the importance of population-based studies to better understand the actual burden of disease in the population. Continuous improvement in cancer registration and the linkage of population-based data with clinical information and laboratory data obtained from patients' medical records and health insurance claims are of paramount importance. The analysis of aggregate data can help clinicians, researchers and policy-makers to better understand the predictors of outcomes after acute leukaemias, as well as the quality of care provided for children, adolescents and young patients with these diseases in California. Eventually, priorities can be set in order to improve survival and decrease the persistent inequalities in health observed among patients with acute leukaemia in California and possibly in other states and nations.

"If we are to preserve civilisation, we must make certain its benefits are available to the many, not reserved for the few."

Dr Raul Ribeiro, N Engl J Med 2005[167]

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Appendix

Appendix 1. Distribution of acute leukaemia by race/ethnicity in California

For acute lymphoblastic (ALL) and promyelocytic (APL) leukaemias there was a predominance of Hispanic patients. For non-APL acute myeloid leukaemia (AML), the proportion of white patients was slightly higher than Hispanic patients (Figure 1A).

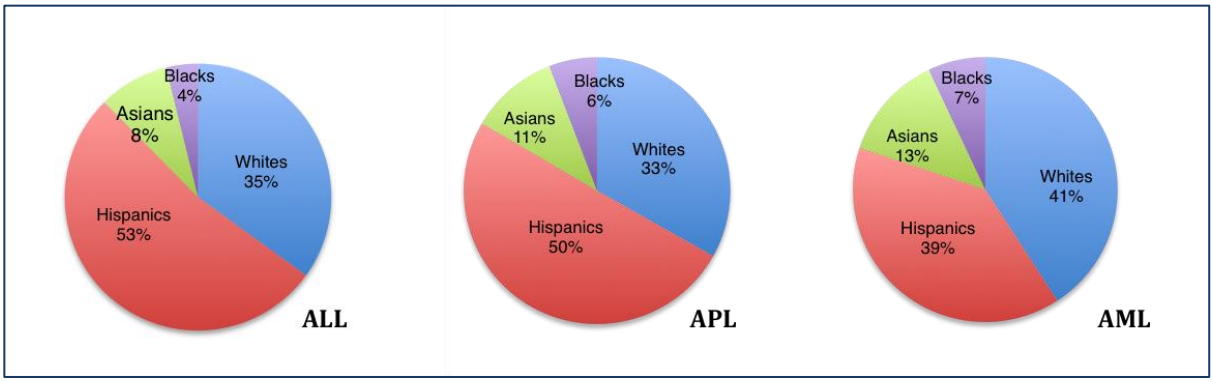

Figure A1: Distribution of patients with acute leukaemias by race/ethnicity in California, 1988–2011. The age range was 0–19 years for acute lymphoblastic leukaemia (ALL) and 0–39 years for acute promyelocytic leukaemia (APL) and non-APL acute myeloid leukaemia (AML).

Appendix 2. SEER/CCR Patient Follow-up Calculation

We assume that Y is the calendar year ending 22 months prior to the due date for the November submission, which is November 1st. [396]

For example: For the November 2012 submission – 22 months prior would be the calendar year **2010**.

Current follow-up percentage (P) is for patients diagnosed during the years **prior** to Y.

For example: prior to Y = 2009 & before

If the last reporting year for SEER submission is 2010, the percent of patients diagnosed though 2010 who have current follow-up (P) is calculated as follows:

P = 100 (D+A) / T, where:

D = the number of cases who died prior to January 1st, Y + 1. D = died **prior** to 2011

A = number of cases with follow-up dates on or after Y +1 (dead & alive in 2011 or above)

T = the total number of patients. This includes A + D + *, where

* = number of cases who were last known alive with follow-up dates prior to January 1st, Y + 1 (prior to January 1st, 2011 = lost to follow-up)

Appendix 3. Ethnicty algorithms used by the California Cancer Registry

The North American Association of Central Cancer Registries (NAACCR) Hispanic (NHIA) and Asian Pacific Islander Identification Algorithm (NHAPIIA)

These algorithms use a combination of NAACCR variables to directly or indirectly classify cases as Hispanic or Asian/Pacific Islander for analytical purposes. The best approach is to directly obtain complete information from the medical record.

The algorithm has been computerized and is available on the NAACCR website (http://www.naaccr.org/). It runs as part of a SAS program (http://www.sas.com). The CCR generates this variable by examining the primary last name, all alias last names, all maiden names, and all death certificate fathers' surnames plus birthplace.

The revised NAACCR Hispanic Identification Algorithm (NHIA) v2.2.1[‡]

*Direct Identification***.** Cases reported as Spanish/Hispanic Origin

Appendices 4–7. Research papers 1–3 and press release

[‡] NAACCR Ethnicity Work Group. *NAACCR Guideline for Enhancing Hispano/Latino Identification: Revised NAACCR Hispano/Latino Identification Algorithm [NHIA v2.2.1].* Springfield, IL: North American Association of Central Cancer Registries; 2009.

Racial/Ethnic and Socioeconomic Disparities in Survival Among Children With Acute Lymphoblastic Leukemia in California, 1988–2011: A Population-Based Observational Study

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Background. Despite advances in treatment, survival from acute lymphoblastic leukemia (ALL) remains lower among non-White children than White children in the US. We investigated the association of race/ethnicity and socioeconomic status (SES) with survival. ***Procedures.*** We analyzed 9,295 Californian children (3,251 Whites, 4,890 Hispanics, 796 Asians, and 358 Blacks) aged ≤19 years diagnosed with a first primary ALL during 1988–2011. We used the Kaplan–Meier method to estimate survival at 1, 5, and 10 years after diagnosis for three calendar periods. Hazard ratios of death for race/ethnicity, SES, and clinical factors were estimated by Cox regression models. ***Results.*** Median follow-up time was 7.4 years (range 0–25 years). Over time, survival after ALL improved steadily, but inequalities persisted across races/ethnicities. Five-year survival (95% confidence interval) was 85.0% (83.6–86.2) for White, 81.4% (78.3–84.0) for Asian, 79.0% (77.8–80.2) for Hispanic, and 74.4% (69.4–78.8) for Black children. In multivariable-adjusted models, the hazard of death was increased by 57% among Black, 38% among Hispanic, and 33% among Asian children compared with White children. Patients residing in the lowest SES neighborhoods at diagnosis had a 39% increased risk of death relative to those living in higher SES neighborhoods. ***Conclusion.*** Despite significant improvements in survival, non-White children and children residing in low SES neighborhoods experienced worse survival even after adjusting for potential confounders. Our findings highlight the need to capture specific information on disease biology, treatment, and treatment adherence to better understand the predictors of lower survival in minority and low SES groups. Pediatr Blood Cancer

Key words: childhood; leukemia; population-based; race/ethnicity; SES; survival

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric neoplasm and the leading cause of death due to disease in children and adolescents aged 1–19 years in the United States (US).[1] Several studies have reported an increase in the incidence of childhood ALL in Europe [2] and the US.[3] Evidence suggests that there may be an inherited genetic predisposition to this disease among different races/ethnicities.[4] Strikingly, genetic factors that increase the susceptibility to ALL appear also to be associated with drug-resistant ALL phenotypes and might, in part, explain the poor survival in certain ethnic groups.[5]

Survival from childhood ALL represents one of the most successful advances in the history of science and medicine. ALL was consistently fatal until the 1950s; however, currently approximately 90% of children can be cured in developed countries.[6] This progress has been attributed largely to the use of effective chemotherapy regimens of variable intensities that are adapted to precise risk stratification and assessment of early treatment response.[6]

Despite the dramatic improvement in the survival of children with ALL in the last four decades, survival has varied widely by race/ethnicity in developed [7] and developing nations.[8] Non-adherence to treatment, lack of access to care, cultural influences,

Abbreviations: ALL, acute lymphoblastic leukemia; CCR, California cancer registry; CCS, California children's services; COG, children's oncology group; CI, confidence interval; CNS, central nervous system; CRLF2, cytokine receptor-like factor 2; DCO, death certificate only; HR, hazard ratio; ICD-O-3, international classification of diseases for oncology, third edition; NCI, national cancer institute; NHAI, non-hispanic American Indian; NOS, not otherwise specified; SEER, surveillance, epidemiology, and end results; SES, socioeconomic status; US, United States

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Conflict of interests: Nothing to declare.

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socioeconomic status (SES), and biologic features have been implicated in these variations.[9] However, the extent to which these factors contribute to survival inequalities remain unclear.

California has the largest and most racially and ethnically diverse population in the US [10] and it has maintained a statewide high-quality, population-based cancer surveillance system since 1988. In this study, we examined how survival after ALL varied by race/ethnicity, SES, and clinical factors in Californian children over a 24-year period. Our population-based study on childhood ALL simultaneously investigates the association of race/ethnicity, neighborhood SES, health insurance, type of treating facility, treatment, and secondary neoplasms as well as factors examined previously (e.g., age, gender, immunophenotype, and calendar period).

METHODS

Patients and Study Design

For this population-based observational study, data were retrieved for children and adolescents aged 0–19 years residing in California when diagnosed with a first, primary ALL from January 1, 1988 through December 31, 2011, and followed for vital status through December 31, 2012. Data were obtained from the California Cancer Registry (CCR), to which all new cases of cancer diagnoses must be reported by state law. The CCR contributes to approximately half of the data in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) and is estimated to include more than 99% of all invasive cancers diagnosed in California. We included the following morphology codes from the *International Classification of Diseases for Oncology*, third edition (ICD-O-3):[11] 9,727, 9,728, 9,729, 9,811, 9,812, 9,813, 9,814, 9,815, 9,816, 9,817, 9,818, 9,835, 9,836, and 9,837. Among 9,429 eligible patients, 9,295 were included for survival analysis. The following patients were excluded from analysis: 7 reported by death certificate only (DCO), 5 reported by autopsy only, 51 for whom race/ethnicity was unknown, 60 of Non–Hispanic American Indian (NHAI) race/ethnicity for whom the small sample size precluded analysis, and 11 with inconsistent dates of diagnosis or follow-up and/or leukemia classification. ALL was morphologically verified in 99.8% of patients, and the percentage of cases with verified vital status on December 31, 2012, was 87.1%.

Institutional review board (IRB) approval—Ethics approval for human subjects research was obtained from the California 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 HIPPA authorization.

Covariates

Covariates included in the analysis were age at diagnosis (<1, 1–4, 5–9, 10–14, and 15–19 years); gender (male, female); race/ethnicity (Non-Hispanic White [White], Non-Hispanic Black [Black], Hispanic, and Non-Hispanic Asian/Pacific Islander [Asian]); immunophenotype (categorized as B-cell, T-cell, or not otherwise specified [NOS] according to the morphology codes); secondary neoplasms; and neighborhood SES. Secondary neoplasm was defined as a new malignancy registered in the CCR after the diagnosis of ALL, following the SEER's multiple primaries rules for hematopoietic diseases.[12] Some types of malignant neoplasms have been associated with worse prognosis [13] and we have controlled for their occurrence in our analyses. Because information on SES at the individual level is not collected by the CCR, a previously developed neighborhood SES measure [14] was used. It is derived from principal components analysis of seven census indicator variables of SES (education level, proportion unemployed and with a blue collar job, proportion below 200% of federal poverty level, and median household income, rent, and home value). This index is based on data at the level of the census block groups and is considered adequate as a surrogate to SES at individual level,[15] and can capture neighborhood-level factors that may affect cancer incidence and outcomes.[16] SES was divided into quintiles based on the statewide distribution and assigned to patients on the basis of their residence at time of diagnosis. Other covariates included type of insurance at time of initial treatment (private, public, no insurance, or unknown) collected from 1996 onwards; calendar period (1988–1995, 1996–2003, 2004–2011); and type of treating hospital. Because the care provided by specialized pediatric oncologic centers may be different from that provided in general hospitals, we identified children's hospitals and pediatric cancer centers in California by using listings from the Children's Hospital Association [17] and the Children's Oncology Group (COG).[18] These hospitals offer clinical trials sponsored by the COG, which is supported by the NCI. On the basis of the cancer reporting facility, patients were classified by whether they had received care at a pediatric cancer center (yes, no). Chemotherapy, radiotherapy, and time to chemotherapy were evaluated in descriptive analyses of treatment. They were not included in the statistical model because of changes in the use of central nervous system (CNS) radiation over time [19] and the widespread use of chemotherapy protocols. Inclusion of treatment in the model did not change the associations observed among race/ethnicity, SES, and survival.

Statistical Analyses

We used the χ^2 test to compare frequency distributions of sociodemographic and clinical characteristics by race/ethnicity. Follow-up time was defined as the date of diagnosis to the date of death from any cause, or censoring at the end of the study period (December 31, 2012) or last known date of follow-up, whichever came first.

We estimated overall survival at 1, 5, and 10 years for each covariate (except chemotherapy and radiation) and calendar period by the Kaplan–Meier method. The log-rank test was used to compare differences in survival across strata. We used unadjusted and multivariable-adjusted Cox regression models to estimate the hazard ratios (HRs) of death with associated 95% confidence interval (CI).

We tested the proportional-hazards assumption by examining log–log survival plots and confirmed the results by using Schoenfeld residuals. There was evidence that age, immunophenotype, and secondary neoplasms violated the proportional hazard assumption, and these were therefore included as stratification variables in the models. Secondary neoplasm was analyzed as a time-dependent variable.

Because information on type of insurance was not routinely collected prior to 1996, we ran three Cox regression models: a model without insurance with all patients, a model without insurance but limited to patients diagnosed from 1996 onwards,

and another model including insurance but limited to patients diagnosed from 1996 onwards. We investigated interactions between racial/ethnic groups and other covariates. Statistical analyses were performed by using the Stata 13 software and a two-sided P-value < 0.05 was considered statistically significant.

RESULTS

Sociodemographic and Clinical Characteristics

Table I shows patients and disease characteristics by race/ethnicity. In the 9,295 patients in our cohort, there was a higher percentage of males (58%) than females (42%). More than half the patients (52%) were Hispanic, followed by White (35%), Asian (9%), and Black (4%). The median age at diagnosis was 4 years for Asian, 5 years for White and Hispanic, and 7 years for Black children. By immunophenotype, 60% of patients had B-cell, 12% had T-cell, and approximately 28% had NOS ALL. The proportion of T-cell ALL was significantly higher in Black (23%) than in White (15%), Asian (13%), and Hispanic (10%) children. White and Asian children were more likely to have private insurance (80% and 74%, respectively) than Black and Hispanic children (53% and 40% respectively). Approximately 1.4% of children were diagnosed with secondary neoplasms, of which 58% were solid and 46% were hematopoietic. The use of CNS radiation decreased progressively from 24% in the first time period to 12% in the last period.

TABLE I. Sociodemographic and Clinical Characteristics of Children (Aged 0–19 Years) With Acute Lymphoblastic Leukemia Diagnosed From 1988 to 2011 and Followed Up to 2012 in California, by Race/Ethnicity

Covariates	Whites N (%)	Blacks N (%)	Hispanics N (%)	Asians N (%)	Total cohort N (%)	P^a
Total	3,251 (35)	358 (4)	4,890 (52)	796 (9)	9,295 (100)	
Age at diagnosis, years						
<1	69 (2.1)	9 (2.5)	158 (3.2)	29 (3.6)	266 (2.9)	
1–4	1,468 (45.2)	117 (32.7)	2,023 (41.4)	382 (48.0)	3,990 (42.9)	
5–9	868 (26.7)	102 (28.5)	1,216 (24.9)	194 (24.4)	2,382 (25.6)	
10–14	465 (14.3)	74 (20.7)	807 (16.5)	101 (12.7)	1,447 (15.5)	
15–19	381 (11.7)	56 (15.6)	686 (14.0)	90 (11.3)	1,213 (13.1)	<0.0001
Median	5	7	5	4	5	
Gender						
Male	1,911 (58.8)	206 (57.5)	2,815 (57.6)	459 (57.7)	5,391 (58.0)	
Female	1,340 (41.2)	152 (42.5)	2,075 (42.4)	337 (42.3)	3,904 (42.0)	0.738
Chemotherapy						
No	44 (1.3)	11 (3.1)	79 (1.6)	7 (0.9)	141 (1.5)	
Yes	3,207(98.7)	347 (96.9)	4,811 (98.4)	789 (99.1)	9,154 (98.5)	0.031
CNS radiation						
No	2,717 (83.6)	275 (76.8)	4,085 (83.5)	687 (86.3)	7,764 (83.5)	
Yes	534 (16.4)	83 (23.2)	805 (16.5)	109 (13.7)	1,531 (16.5)	0.001
Treatment at a pediatric cancer center						
No	931 (28.6)	131 (36.6)	1,571 (32.1)	240 (30.1)	2,873 (30.9)	
Yes	2,320 (71.4)	227 (63.4)	3,319 (67.9)	556 (69.9)	6,422 (69.1)	0.001
Leukemia immunophenotype						
T-cell	483 (14.9)	84 (23.4)	464 (9.5)	102 (12.8)	1,133 (12.2)	
B-cell	1,736 (53.4)	176 (49.2)	3,183 (65.1)	490 (61.6)	5,585 (60.1)	
NOS	1,032 (31.7)	98 (27.4)	1,243 (25.4)	204 (25.6)	2,581 (27.7)	<0.0001
Secondary neoplasms						
No	3,209 (98.7)	356 (99.4)	4,838 (98.9)	782 (98.2)	9,185 (98.8)	
Yes	42 (1.3)	2 (0.6)	52 (1.1)	14 (1.8)	110 (1.2)	0.223
Socioeconomic status						
1. Lowest 20%	247 (7.6)	96 (26.8)	2,067(42.2)	102 (12.8)	2,513 (27.0)	
2	532 (16.4)	109 (30.5)	1,256 (25.7)	120 (15.1)	2,020 (21.7)	
3	683 (21.0)	66 (18.4)	831 (17.0)	139 (17.5)	1,723 (18.5)	
4	847 (26.0)	58 (16.2)	479 (9.8)	200 (25.1)	1,585 (17.1)	
5. Highest 20%	942 (29.0)	29 (8.1)	257 (5.3)	235 (29.5)	1,463 (15.7)	<0.0001
Calendar period						
1988–1995	1,169 (35.9)	104 (29.0)	1,162 (23.8)	222 (27.9)	2,657 (28.6)	
1996–2003	1,093 (33.6)	127 (35.5)	1,670 (34.1)	270 (33.9)	3,160 (34.0)	
2004–2011	989 (30.4)	127 (35.5)	2,058 (42.1)	304 (38.2)	3,478 (37.4)	<0.0001
Type of health insurance: limited to cases diagnosed from 1996 onwards (N = 6638)						
No insurance	14 (0.7)	9 (3.5)	106 (2.9)	4 (0.7)	133 (2.0)	
Private insurance	1,669 (80.1)	135 (53.2)	1,493 (40.0)	425 (74.0)	3,722 (56.1)	
Public insurance	341 (16.4)	101 (39.8)	1,997 (53.6)	128 (22.3)	2,567 (38.7)	
Unknown	58 (2.8)	9 (3.5)	132 (3.5)	17 (3.0)	216 (3.2)	<0.0001

CNS, central nervous system; NOS, not otherwise specified. [a]χ^2 P-value.

Chemotherapy was administered to more than 98% of children, of whom at least 95% received chemotherapy within 2 weeks of diagnosis.

Survival

Table II displays survival probabilities at 1, 5, and 10 years, by sociodemographic and clinical characteristics. Figures 1 and 2 show survival by race/ethnicity and SES, respectively. The median follow-up time was 7.4 years (range 0–25 years). By the end of the study period, 1,955 study patients died. Survival improved steadily over calendar time but was persistently lower for Black, Hispanic, and Asian children than for White children. Differences in survival were most striking between Black and White children.

Unadjusted and Multivariable Analyses

In the unadjusted model all variables were associated with significant increased hazard of death. After multivariable adjustment, our analysis revealed that the HRs of death were still significant for race/ethnicity and SES (Table III). The hazard of death was increased by 57% (HR = 1.57 [1.26–1.96]) among Black,

TABLE II. Overall Survival With 95% Confidence Intervals for Acute Lymphoblastic Leukemia at 1, 5, and 10 Years After Diagnosis in Children (0–19 Years Old) in California From 1988 to 2011, by Sociodemographic and Clinical Factors

Covariates	1-year survival (95%CI)	5-year survival (95%CI)	10-year survival (95%CI)
All children	94.5 (94.0–95.0)	81.2 (80.3–82.0)	77.1 (76.1–78.0)
Age at diagnosis			
<1	76.9 (71.3–81.6)	50.2 (43.7–56.2)	45.7 (39.1–52.1)
1–4	97.9 (97.4–98.3)	89.3 (88.2–90.3)	86.3 (85.1–87.4)
5–9	96.6 (95.8–97.3)	86.2 (84.7–87.6)	80.7 (78.8–82.4)
10–14	91.8 (90.2–93.1)	73.5 (71.0–75.7)	69.0 (66.3–71.5)
15–19	86.3 (84.2–88.1)	60.2 (57.2–63.0)	55.8 (52.6–58.8)
Log-rank test *P*-value<0.00001			
Race/ethnicity			
White	95.8 (95.0–96.4)	85.0 (83.6–86.2)	81.5 (80.0–82.9)
Black	91.8 (88.4–94.2)	74.4 (69.4–78.8)	70.7 (65.3–75.4)
Hispanic	93.9 (93.2–94.5)	79.0 (77.8–80.2)	74.4 (73.0–75.7)
Asian	94.4 (92.6–95.8)	81.4 (78.3–84.0)	77.4 (74.0–80.4)
Log-rank test *P*-value<0.00001			
Gender			
Male	94.3 (93.7–94.9)	79.5 (78.3–80.6)	75.1 (73.8–76.3)
Female	94.7 (94.0–95.4)	83.5 (82.2–84.7)	79.9 (78.4–81.2)
Log-rank test *P*-value<0.00001			
Leukemia immunophenotype			
B-cell	95.4 (94.8–95.9)	82.7 (81.6–83.7)	77.8 (76.5–79.0)
T-cell	90.8 (88.9–92.3)	73.8 (71.0–76.3)	71.0 (68.0–73.7)
NOS	94.3 (93.3–95.1)	81.1 (79.5–82.6)	77.8 (76.1–79.4)
Log-rank test *P*-value<0.00001			
Calendar period			
1988–1995	93.0 (91.9–93.9)	76.9 (75.2–78.5)	72.8 (71.1–74.5)
1996–2003	94.8 (93.9–95.5)	80.7 (79.3–82.1)	76.7 (75.1–78.1)
2004–2011	95.5 (94.7–96.1)	85.7 (84.3–87.0)	N/A
Log-rank test *P*-value<0.00001			
Socioeconomic status			
1. Lowest 20%	93.5 (92.4–94.4)	77.0 (75.3–78.7)	72.5 (70.5–74.3)
2	94.5 (93.4–95.5)	81.5 (79.6–83.2)	77.8 (75.6–79.6)
3	94.5 (93.3–95.4)	82.3 (80.3–84.1)	78.4 (76.2–80.5)
4	95.3 (94.1–96.2)	82.2 (80.1–84.1)	78.2 (75.9–80.3)
5. Highest 20%	95.5 (94.3–96.4)	85.4 (83.3–87.1)	81.3 (78.9–81.6)
Log-rank test *P*-value<0.00001			
Treatment at a pediatric cancer center			
No	92.9 (91.9–93.8)	77.0 (75.4–78.6)	73.2 (71.4–74.9)
Yes	95.2 (94.7–95.7)	83.0 (82.0–84.0)	78.9 (77.7–80.0)
Log-rank test *P*-value = 0.0014			
Type of health insurance: limited to cases diagnosed from 1996 onwards (N = 6638)			
No insurance	93.3 (88.1–96.9)	77.6 (68.9–84.1)	74.2 (64.4–81.6)
Private insurance	96.6 (94.9–96.2)	85.2 (83.9–86.4)	81.8 (80.3–83.2)
Public insurance	94.8 (93.9–96.5)	81.5 (79.9–83.1)	76.3 (74.3–78.3)
Unknown	91.6 (87.0–94.6)	66.2 (59.3–72.2)	63.0 (55.8–69.3)
Log-rank test *P*-value<0.00001			

CI, confidence interval; NOS, not otherwise specified; N/A, not applicable.

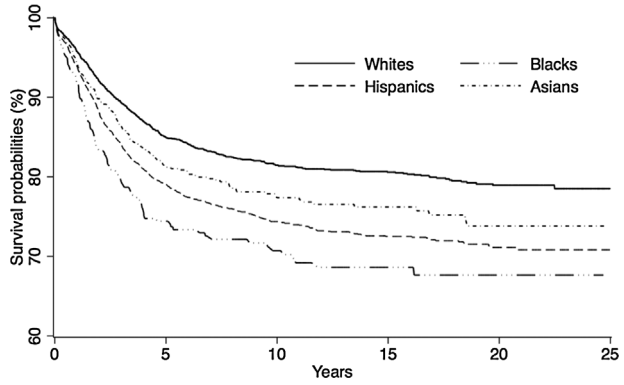

Fig 1. Overall survival by race/ethnicity among children (0–19 years old) diagnosed with acute lymphoblastic leukemia in California, 1988–2011.

38% (HR = 1.38 [1.23–1.55]) among Hispanic, and 33% (HR = 1.33 [1.12–1.59]) among Asian children compared with White children. Patients residing in the lowest SES neighborhoods were at 39% (HR = 1.39 [1.18–1.64]) increased risk of death than those in the higher SES neighborhoods. After controlling for other covariates, the hazard of death was not associated with the type of hospital in which children were treated or with type of insurance for patients diagnosed from 1996 onwards. Insurance minimally attenuated the HRs for race/ethnicity and SES among patients diagnosed from 1996 onwards (Table III). In addition, the inclusion of SES in our model did not substantially change the racial/ethnic differences in survival that we observed. There were no significant interactions between race/ethnicity, SES, calendar period, and other study covariates.

DISCUSSION

In our large population-based study of nearly 10,000 children with ALL, survival for Black, Hispanic, and Asian children was lower than that for White children. The survival differences we observed in our cohort persisted over time and were most marked between Black and White children. In contrast to previous studies reporting that survival of Asian children was similar to [20] or better [21] than for White, Hispanic, and Black children, our study showed that Asian children in California had lower survival than White children with ALL. Our results are consistent with a previous study [7] that also used US population-based data, but we extended their findings by additionally investigating neighborhood SES, secondary neoplasms, type of insurance, treatment, and treating facility.

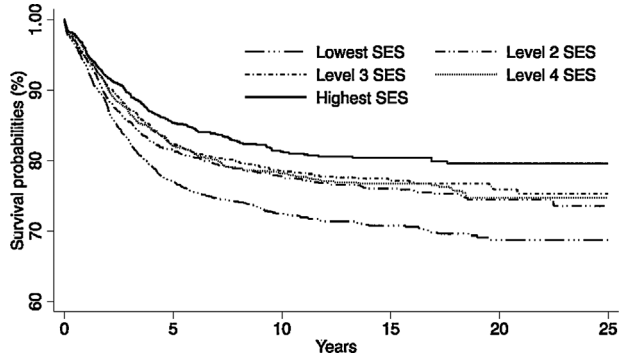

Fig 2. Overall survival by socioeconomic status among children (0–19 years old) diagnosed with acute lymphoblastic leukemia in California, 1988–2011.

Genetic and non-genetic factors help to explain disparities in cancer survival. Our population-based study allowed the investigation of non-genetic factors and found that neighborhood SES had a significant, independent association with survival, particularly when comparing children residing in the highest and lowest SES neighborhoods. The inclusion of SES in our statistical model did not substantially change the racial/ethnic differences in survival that we observed, suggesting that other factors underlie these survival disparities. Our SES finding is consistent with previous studies of poorer survival among financially deprived populations.[22]

White and Asian children were more likely than Hispanic and Black children to have private insurance, but the type of insurance did not significantly affect survival after ALL after adjustment for other variables. Insurance may have not been associated with survival because, in California, patients younger than 21 years are eligible for California Children's Services (CCS), a state program that offers insurance for chronic and complex diseases and covers all children with cancer with or without insurance. Although the CCS program ensures that all children with ALL have access to care, this may not be sufficient in the long-term for children with low SES. Differences in relapse rates among children from different racial/ethnic groups have been observed. In a study on adherence to oral 6-mercaptopurine during the maintenance phase of ALL treatment, non-adherence was significantly higher among non-White children than White children and it considerably increased relapse rates. Sociodemographic characteristics also played a significant role in adherence to treatment.[22]

Although past evidence suggests that children with ALL treated at specialized pediatric cancer centers had better survival than those at general hospitals,[23] our study did not find survival differences by treating facility. Because the treating facility typically refers to the hospital that initially diagnosed and/or treated the patient, it is possible that some children admitted in non-specialized pediatric hospitals were later referred to pediatric cancer centers where standardized COG protocols were used, thus confounding our results.

ALL is a lethal disease if treatment is not started promptly. Although the lack of appropriate chemotherapy agents might contribute to the lower survival in Eastern Europe,[24] our examination of the proportion of children treated with chemotherapy and time from diagnosis to the start of treatment showed that the majority of study patients were treated within the first 2 weeks of diagnosis. However, late diagnosis might have had an adverse effect on outcome. Parents who are undocumented immigrants or of lower SES may wait longer to seek medical care for their children or may do so when the child is already severely sick. Late diagnosis may increase the risk of (early) death [25–27] because patients may develop severe infectious and/or metabolic complications prior to referral to a specialized cancer center.[28] However, we did not have sufficient information to evaluate this possibility.

Our data indicate that the use of prophylactic cranial irradiation has decreased markedly over time, suggesting protocol adherence to the new recommendations for using systemic and intrathecal therapy instead of radiation for children with high-risk CNS relapse. This recommendation aims to prevent late radiation-related complications such as second neoplasms.[29] Infants and older

TABLE III. Unadjusted and Multivariable-Adjusted Hazard Ratios and 95% Confidence Intervals for Overall Survival in Children (0–19 Years Old) With Acute Lymphoblastic Leukemia in California.

Covariates	Death N (%)	Unadjusted HR1 (1988–2011) (95%CI)	Adjusted HR2 (1988–2011) (95%CI)	Adjusted HR3 (1996–2011) (95%CI)	Adjusted HR4 (1996–2011) (95%CI)
Race/ethnicity					
White	568 (29.1)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Black	100 (5.1)	1.78 (1.44–2.20)	1.57 (1.26–1.96)	1.74 (1.31–2.31)	1.72 (1.29–2.28)
Hispanic	1,123 (57.4)	1.47 (1.33–1.62)	1.38 (1.23–1.55)	1.43 (1.22–1.68)	1.37 (1.17–1.62)
Asian	164 (8.4)	1.26 (1.06–1.50)	1.33 (1.12–1.59)	1.42 (1.13–1.79)	1.40 (1.11–1.76)
Gender					
Male	1,237 (63.3)	1.27 (1.16–1.39)	1.19 (1.09–1.31)	1.20 (1.06–1.35)	1.19 (1.06–1.35)
Female	718 (36.7)	1.0 (Reference)	1.0 (Reference)	1.00 (Reference)	1.00 (Reference)
Socioeconomic status					
1.Lowest 20%	623 (32.3)	1.61 (1.39–1.87)	1.39 (1.18–1.64)	1.40 (1.12–1.75)	1.30 (1.04–2.27)
2.	414 (21.2)	1.29 (1.10–1.51)	1.15 (0.97–1.35)	1.20 (0.95–1.51)	1.15 (0.91–1.44)
3.	339 (17.3)	1.20 (1.02–1.41)	1.13 (0.95–1.33)	1.10 (0.87–1.38)	1.06 (0.84–1.34)
4.	324 (16.6)	1.23 (1.04–1.45)	1.17 (0.99–1.39)	1.22 (0.97–1.54)	1.20 (0.95–1.51)
5. Highest 20%	246 (12.6)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Calendar period					
1988–1995	781 (39.9)	1.66 (1.47–1.87)	1.97 (1.74–2.24)	N/A	N/A
1996–2003	744 (38.1)	1.38 (1.22–1.56)	1.50 (1.33–1.70)	1.52 (1.34–1.73)	1.50 (1.33–1.71)
2004–2011	430 (22.0)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Treatment at a pediatric cancer center					
No	724 (37.0)	1.35 (1.23–1.48)	1.06 (0.96–1.16)	1.05 (0.92–1.19)	1.05 (0.92–1.19)
Yes	1,231 (63.0)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Type of health insurance: model limited to cases diagnosed from 1996 onwards (N = 6638)					
No insurance	29 (2.5)	1.54 (1.06–2.23)	N/A	N/A	1.22 (0.83–1.89)
Private insurance	583 (49.6)	1.00 (Reference)	N/A	N/A	1.00 (Reference)
Public insurance	487 (41.5)	1.31 (1.16–1.47)	N/A	N/A	1.15 (1.01–1.32)
Unknown	75 (6.4)	2.31 (1.82–2.94)	N/A	N/A	1.77 (1.38–2.26)

HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified. The multivariable models were adjusted for all variables presented in the table and stratified by age, immunophenotype and secondary neoplasm. HR1, unadjusted model; Hr2, adjusted model without insurance, 1988–2011; Hr3, adjusted model without insurance, 1996–2011; Hr4, adjusted model with insurance, 1996–2011.

children had significant lower survival than did children aged 1–9 years, supporting findings in previous studies in Europe [30] in the US.[1]

The treatment of childhood leukemia is complex, expensive, and lengthy (2.5–3 years). With modern supportive care, fewer than 10% of deaths among children with ALL are due to therapy-associated toxicity,[31] and disease relapse remains the leading cause of death.[32] Although relapsed ALL is treated with curative intent in the US, the long-term survival of children who relapse is only approximately 25%, even when bone marrow transplant is available.[32] Multiple factors might affect the survival of children with ALL, and this can be a complex construct involving socioeconomic and cultural variables.[22]

Differences in disease biology may explain, in part, the persistent gap in survival by race/ethnicity. For example, in our study, survival differences were more marked between Black and White children (Fig. 1, Table II). Intrinsic biologic features may partially explain this observation. Previous studies reported that compared to White children, Black children with ALL had a higher incidence of unfavorable features, including high leukocyte count, higher proportion of T-cell leukemia, chromosome translocations [e.g. t(1,19)], and molecular abnormalities associated with an increased risk of relapse.[33] In contrast, approximately 50% of White children have ALL with favorable genetic features (B-cell ALL), which translate to excellent prognosis.[4] Pui et al.[34] reported that survival rate of Black children receiving intensive risk-based therapy and comprehensive supportive care can be similar to that of White children, thereby reducing the impact of these adverse factors. However, to our knowledge, these results found at a single institution, have not been replicated.

Intrinsic biologic differences may also play an important role in the poor prognosis of ALL among Hispanic children. A recent review [9] of the genomic profiling of ALL associated with susceptibility and outcome among Hispanic children identified a novel subtype of ALL called Philadelphia chromosome-like (Ph-like) ALL among these children. The incidence of Ph-like ALL in Hispanic children is significantly higher (35%) than in non-Hispanic children (7%). Approximately 50% of children with this subtype overexpress the somatic cytokine receptor-like factor 2 (*CRLF2*).[33] Furthermore, Perez-Andreu et al.[35] demonstrated that inherited GATA binding protein 3 (GATA3) variants are also overrepresented among Hispanics and increase the susceptibility to Ph-like ALL. The presence of both these variants is associated with a higher risk of relapse among Hispanic children with ALL and may in part explain their poor response to treatment.

Our study has some limitations. Data on specific genetic abnormalities have only been collected by the CCR since 2010. Because of the small size of this group, we could not compare the survival of children on the basis of genetic characteristics. However, this will be of interest in future studies. Most children and adolescents with ALL in California are treated at pediatric cancer centers that use COG protocols, but we do not have information

about which patients are treated with these protocols and the intensity of treatment administered. We lacked data on relapse rates, as disease recurrence is not routinely collected by population-based cancer registries.

The strengths of our study include the use of a high-quality population-based dataset, a large sample of an ethnically and racially diverse population, and long period of post-diagnostic observation that allowed us to examine trends in outcome. Our study covered nearly the entire population of children and adolescents diagnosed with ALL in California and provided information on numerous factors such as neighborhood SES, insurance, treatment, treating facility, secondary neoplasm, and immunophenotype as well as age, gender, and calendar period.

In summary, despite the remarkable improvement in cure rates after ALL, non-White children and children in low SES neighborhoods have been disproportionally dying even when access to high-quality care is available and standardized protocols are followed. In the coming years, genomic findings will dramatically change the prognostic classification of ALL. In the era of precision medicine, the value of population-based cancer registries can be improved by collaborating with pediatric oncologists and cancer registries from COG-affiliated hospitals. Capturing specific biologic (e.g., ALL genomic signature, minimal residual disease, blast chromosomal abnormalities, presenting white counts, and NCI risk grouping), and socioeconomic (e.g., treatment adherence) information can help to identify predictors of racial/ethnic differences in treatment failure and guide the development of interventions aimed at improving survival for minority and low SES children with ALL.

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Author Contribution

RA and DYL performed and RK advised on the statistical analyses. DYL, RCR, SLG, RK, RMG, and NMM interpreted the data and drafted and critically reviewed the manuscript. RA and THMK designed the study, interpreted the data, and led the writing and review of the manuscript. All authors read and approved the final manuscript.

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Original Article

Disparities in Early Death and Survival in Children, Adolescents, and Young Adults with Acute Promyelocytic Leukemia in California

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BACKGROUND: Findings from clinical trials and population-based studies have differed with regard to whether mortality within 30 days of diagnosis (early death) of acute promyelocytic leukemia (APL) has decreased in the era of all-*trans* retinoic acid and anthracycline-based chemotherapy. **METHODS:** Using data from the California Cancer Registry, the authors investigated 7-day and 30-day mortality and survival in 772 patients who were aged birth to 39 years when they were diagnosed with APL during 1988 to 2011. Logistic regression and Cox proportional models were used to examine the association of early death and survival, respectively, with sociodemographic and clinical factors. **RESULTS:** The overall 30-day mortality decreased significantly over time, from 26% (1988-1995) to 14% (2004-2011) (P =.004). On multivariable analysis, the odds of 30-day mortality were 3 times as high during 1988 through 1995 than 2004 through 2011 (P =.001). However, 7-day mortality did not improve over time (P =.229). When patients who died within 7 days of diagnosis were excluded, the 30-day mortality during 1996 to 2011 was 3% to 8%, which is similar to levels reported in clinical trials. Higher early death and lower survival were associated with a lack of health insurance (1996-2011) (early death odds ratio, 2.67; P =.031) and Hispanic race/ethnicity (early death odds ratio, 2.13; P =.014). Early death was not found to be associated with age, sex, socioeconomic status, or hospital type. Black patients also experienced worse survival. **CONCLUSIONS:** The findings of the current study revealed a decreased 30-day mortality during the all-*trans* retinoic acid era, but 7-day mortality remained high. Efforts to achieve equal outcomes in young patients with APL should focus on improving access to effective treatment, mainly among uninsured patients and those of Hispanic and black race/ethnicity. ***Cancer*** **2015;121:3990-7**. © *2015 American Cancer Society.*

KEYWORDS: acute promyelocytic leukemia, adolescents, all-*trans* retinoic acid (ATRA), children, early death, health disparities, health insurance, survival, young adults.

INTRODUCTION

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) that carries the PML/RAR-α fusion in >90% of cases. Bleeding and thrombosis are frequent and can be aggravated by cytotoxic chemotherapy, resulting in early death due mainly to intracranial hemorrhage.[1]

An estimated 600 to 800 new cases of APL (4%-13% of AML cases) occur annually in the United States, most frequently in adults.[2,3] Although APL was once highly fatal, the addition of all-*trans* retinoic acid (ATRA) to anthracycline-based chemotherapy and the introduction of arsenic trioxide (arsenic) have dramatically improved outcomes; currently, 95% to 100% of patients with APL achieve complete remission.[4,5] Moreover, arsenic has become the treatment of choice for patients with recurrent APL after frontline treatment with ATRA and chemotherapy.[6]

ATRA and arsenic rapidly reduce the risk of hemorrhage and should be initiated as soon as APL is suspected.[7] ATRA was approved by the US Food and Drug Administration (FDA) in November 1995 and arsenic received FDA approval in

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September 2000. During the ATRA era, early death has decreased overall, from approximately 20%[8,9] to 5% to 10%.[10] However, early death remains high in the United States[11,12] and Europe,[13] implicating factors other than ATRA.

Because recent studies have examined early death and survival in patients aged ≥15 years[11,13,14] and there are few reports of population-based studies in young patients with APL (see Supporting Information Table S1), we investigated early death and survival in patients in California who were diagnosed between birth and age 39 years over a 25-year period, and assessed the association of sociodemographic and clinical factors with these outcomes.

MATERIALS AND METHODS

Patient Selection

Data were obtained from the California Cancer Registry, to which reporting is mandatory and completeness of cases is at least 98%.[15] We identified all patients with a first, primary APL diagnosed between birth and age 39 years during 1988 through 2011 and followed until December 31, 2012. APL was diagnosed as histology code 9866 in the *International Classification of Diseases for Oncology, 3rd Edition*.[16] Of 784 patients identified, 4 were excluded due to a missing date of diagnosis and 8 due to unknown or Native American (small subgroup) race/ethnicity. The current study included 772 patients.

Institutional Review Board Approval

Ethics approval for human subjects research was obtained from the Institutional Review Board of the Cancer Prevention Institute of California. Because 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.

Variables

The variables examined for their association with APL outcomes were age at diagnosis, categorized as 4 groups based on progressive decrements in survival[17] (birth-9 years, 10-19 years, 20-29 years, and 30-39 years); sex; era of diagnosis according to ATRA approval by the US FDA (pre-ATRA era [1988-1995], earlier ATRA era [1996-2003], and later ATRA era [2004-2011]); race/ethnicity (non-Hispanic white [white], non-Hispanic black [black], Hispanic, and non-Hispanic Asian/Pacific Islander [Asian]); initial care at hospitals affiliated with National Cancer Institute-designated cancer centers; type of health insurance at the time of admission (routinely documented starting in 1996) (none, public, private, or unknown/not otherwise specified); and neighborhood socioeconomic status (SES) based on block-level census data. Neighborhood SES quintiles based on statewide distribution have been used extensively in California.[18]

Information regarding hospital designation was obtained from the initial reporting facility. There were no data regarding the intensity of treatment or drugs used (conventional genotoxic chemotherapy, ATRA and/or arsenic).

Statistical Analysis

We used univariable and multivariable logistic regression to investigate the association of the sociodemographic and clinical factors with 7-day and 30-day mortality through estimation of the odds ratios (ORs) and associated 95% confidence intervals (95% CIs). We analyzed 30-day mortality with and without patients who died within 7 days. We estimated overall survival (all-cause survival) at 1 year and 5 years using the Kaplan-Meier method, and compared differences in survival across strata for each variable using the log-rank test. We used univariable and multivariable Cox regression models to examine the association of sociodemographic and clinical factors with the risk of death through estimation of the hazard ratios and associated 95% CIs. Schoenfeld residuals were used to assess the proportional hazard assumptions. We tested for interactions between calendar periods, age groups, neighborhood SES, and race/ethnicity. All statistical analyses were performed by using Stata 13 statistical software (StataCorp, College Station, Tex). A 2-sided $P<.05$ was considered statistically significant.

RESULTS

Approximately 16% of all AML cases in the registry were APL, the majority of which (79%) were diagnosed during the ATRA era (after 1995). According to death certificates, most patients died of leukemia (228 patients; 90%); a much smaller percentage of patients died of other (17 patients; 7%) or unknown (7 patients; 3%) causes. Fewer than 2% of patients died of complications of APL treatment, such as infection (2 patients), renal dysfunction (1 patient), or heart failure (1 patient). Table 1 summarizes patient characteristics.

Early Death

Among patients who experienced early death, the median age at diagnosis was 29 years; 82 of these patients (11%) died within 7 days and 133 (17%) died within 30 days of diagnosis. Thirty-day mortality decreased significantly

TABLE 1. Patient Characteristics, Early Mortality, and Overall Survival

Characteristic		7-Day Mortality (%)	P^a	30-Day Mortality (%)	P^a	1-Year OS (%)	5-Year OS (%)	P^b
Total[c]	772 (100)	82 (11.0)		133 (17.2)		78.0 (74.9–80.8)	68.1 (64.6–71.4)	
Calendar period								
1988–1995 (pre-ATRA)	163 (21.1)	22 (13.5)		42 (25.8)		61.7 (53.7–68.7)	46.7 (38.9–54.2)	
1996–2003 (earlier ATRA era)	266 (34.5)	22 (8.3)		43 (16.2)		78.9 (73.5–83.4)	70.1 (64.2–75.2)	
2004–2011 (later ATRA era)	343 (44.4)	38 (11.1)	.229	48 (14.0)	.004	85.1 (80.9–88.5)	77.3 (72.1–81.9)	<.0001
Age at diagnosis, y								
Birth to 9	50 (6.5)	2 (4.0)		4 (8.0)		84.0 (70.5–91.2)	71.8 (57.1–82.3)	
10–19	172 (22.3)	17 (9.9)		26 (15.1)		81.4 (74.7–86.5)	69.8 (62.1–76.2)	
20–29	225 (29.1)	27 (12.1)		38 (16.9)		79.9 (74.0–84.6)	73.2 (66.7–78.6)	
30–39	325 (42.1)	36 (11.1)	.396	65 (20.0)	.152	74.0 (68.9–78.5)	63.1 (57.4–68.3)	.023
Median, 27								
Race/ethnicity								
White	256 (33.2)	20 (7.8)		32 (12.5)		82.8 (77.6–86.9)	72.2 (66.1–77.4)	
Black	45 (5.8)	7 (15.6)		9 (20.0)		73.3 (57.9–83.9)	56.6 (40.6–69.9)	
Hispanic	388 (50.3)	46 (12.4)		79 (20.4)		74.9 (70.2–87.6)	66.5 (61.4–71.1)	
Asian	83 (10.7)	9 (12.1)	.266	13 (15.7)	.070	80.6 (70.2–87.6)	69.2 (57.5–78.3)	.068
Sex								
Male	391 (50.7)	51 (13.3)		77 (19.7)		75.0 (70.4–79.0)	63.1 (57.8–67.8)	
Female	381 (49.3)	31 (8.7)	.028	56 (14.7)	.066	81.1 (76.8–84.7)	73.2 (68.3–77.4)	.005
Initial care at hospitals affiliated with NCI-designated cancer centers								
NCI	155 (20.1)	11 (7.1)		20 (12.9)		81.2 (74.0–86.5)	73.1 (65.2–79.6)	
Non-NCI	617 (79.9)	71 (11.4)	.120	113 (18.3)	.111	77.2 (73.7–80.3)	66.8 (62.8–70.5)	.078
Neighborhood SES, quintile								
1. Lowest 20%	216 (28.0)	26 (12.2)		42 (19.4)		75.3 (69.0–80.5)	66.3 (59.4–72.3)	
2.	168 (21.8)	24 (14.0)		35 (20.8)		74.9 (67.5–80.8)	66.5 (58.6–73.3)	
3. Middle 20%	151 (19.6)	12 (7.8)		24 (15.9)		78.8 (71.3–84.5)	66.9 (58.5–74.0)	
4.	128 (16.6)	13 (10.2)		19 (14.8)		81.2 (73.3–87.0)	73.1 (64.2–80.1)	
5. Highest 20%	109 (14.1)	7 (6.4)	.187	13 (11.9)	.275	83.5 (75.1–89.2)	70.0 (59.9–77.9)	.425
Health insurance (only patients diagnosed in 1996–2011 [n = 609])								
None	45 (7.4)	14 (31.8)		19 (42.2)		53.1 (37.6–66.4)	50.6 (35.2–64.2)	
Public	212 (34.8)	16 (7.4)		23 (10.9)		86.8 (81.4–90.7)	77.2 (70.6–82.5)	
Private	294 (48.3)	27 (9.2)		45 (15.3)		82.0 (77.1–85.9)	74.4 (68.8–79.1)	
Unknown/NOS	58 (9.5)	3 (5.1)	<.0001	4 (6.9)	<.0001	91.2 (80.2–96.3)	79.2 (65.5–88.0)	0.0001

Abbreviations: ATRA, all-*trans* retinoic acid; NCI, National Cancer Institute; NOS, not otherwise specified; OS, overall survival; SES, socioeconomic status.
[a] Chi-square *P* value for testing whether early death differed among groups for each variable.
[b] Log-rank *P* value comparing differences in survival across strata for each variable.
[c] Three patients were excluded due to missing day of diagnosis.

over the 3 eras from 26% in 1988 to 1995 (pre-ATRA) to 16% in 1996 to 2003 (earlier ATRA era) to 14% in 2004 to 2011 (later ATRA era) ($P = .004$) (Table 1) (Fig. 1). However, 7-day mortality showed no evidence of a significant decrease. On multivariable analysis (Table 2), the odds of 30-day mortality differed significantly between 1988 to 1995 and later eras ($P = .001$), but not between the eras of 1996 to 2003 and 2004 to 2011. Hispanic patients had a risk of 30-day mortality that was approximately twice that of white patients. After 1995, type of health insurance was found to be significantly associated with both 7-day and 30-day mortality; the risk of 30-day mortality was approximately 3 times as high in uninsured as in privately insured patients (OR, 2.67; 95% CI, 1.10-6.52). Early death was not found to differ significantly between patients with private versus public insurance ($P = .243$).

When patients with 7-day mortality (82 patients) were excluded from analysis, the 30-day mortality decreased from 15% during 1988 through 1995 to 8% during 1996 through 2003 and 3% during 2004 through 2011 ($P < .0001$; data not shown). There was no evidence of interactions between any variables.

Survival

During 0 to 25 years of follow-up (median in entire cohort, 4.4 years), approximately 33% of patients (252 patients) died. Five-year survival increased from 46.7% during 1988 to 1995 to 70.1% during 1996 to 2003 and 77.3% during 2004 to 2011 ($P < .0001$) (Table 1). Based on the log-rank test, a lower survival estimate was significantly associated with an earlier period of diagnosis, male sex, older age at diagnosis, and lack of health insurance (Table 1). On univariable analyses, survival was lower in Hispanic and black patients versus white patients and uninsured versus insured patients. In multivariable models, the era between 1988 and 1995, black and Hispanic

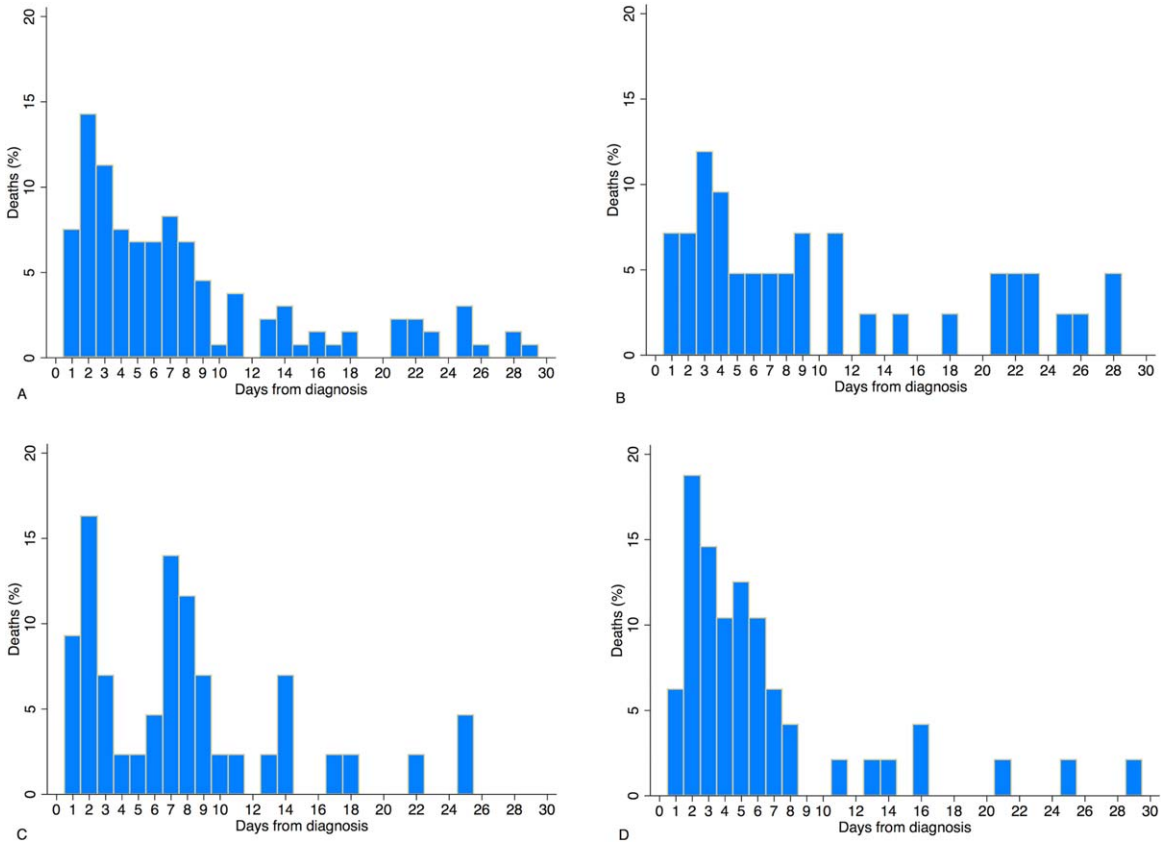

Figure 1. Early death from acute promyelocytic leukemia in California after diagnosis between ages birth to 39 years. (A) Entire study period (1988-2011). (B) Era prior to all-*trans* retinoic acid (pre-ATRA) (1988-1995). (C) Earlier ATRA era (1996-2003). (D) Later ATRA era (2004-2011). Ten patients who died on the day of diagnosis were considered to have a survival time of 1 day.

race/ethnicity, and lack of health insurance remained significantly associated with the hazard of death (Table 3). There was no evidence of a difference in the hazard ratio between patients with private versus those with public insurance ($P = .999$). There was no evidence of violation of the Cox proportional hazard assumptions or of interactions between any variables.

When we excluded patients who died within 30 days of diagnosis in 1996 through 2011, the 5-year survival increased from 77.8% (95% CI, 70.7%-83.3%) to 88.8% (95% CI, 82.4%-93.0%) among patients aged birth to 19 years, and from 72.5% (95% CI, 67.8%-76.6%) to 86.3% (95% CI, 81.9%-89.7%) among patients aged 20 to 39 years (data not shown).

DISCUSSION

In the current population-based study, which spanned 25 years, 30-day mortality decreased significantly after 1995, coinciding with the introduction of ATRA and guidelines recommending aggressive blood product support and intensive infection prophylaxis and treatment for suspected APL. Nevertheless, 30-day mortality remained higher than that observed in patients with non-APL subtypes of AML,[19] and 7-day mortality did not improve over time. The findings of the current study suggest that factors other than ATRA contributed to early death; these may include the timing of diagnosis or chemotherapy, hospital availability of ATRA/arsenic during the critical first 2 to 3 days after diagnosis, adequate blood products, and infection prophylaxis and treatment. A recent study of randomly selected hospitals in the United States found that <50% had ATRA, and one of the main barriers to availability was the absence of ATRA on their formularies.[20]

Patients who experienced an early death most likely lacked early access to effective treatment and/or were too ill when admitted; 10 patients in the current study died on the day of diagnosis. The FDA's approval of ATRA (and later arsenic) may not have resulted in the wide or timely availability of these drugs across all hospitals in California.

TABLE 2. Relation of Sociodemographic and Clinical Factors with 30-Day Mortality

Factor	OR for 30-Day Mortality			
	Unadjusted OR1 (95% CI) (1988–2011)	Adjusted OR2 (95% CI) (1988–2011)	Adjusted OR3 (95% CI) (1996–2011)	Adjusted OR4 (95% CI) (1996–2011)
Calendar period				
1988–1995 (pre-ATRA)	2.18 (1.37–3.46)	3.01 (1.66–5.46)	NA	NA
1996–2003 (earlier ATRA era)	1.20 (0.77–1.87)	1.39 (0.80–2.43)	1.41(0.81–2.46)	1.30 (0.74–2.30)
2004–2011 (later ATRA era)	1 (base)	1 (base)	1 (base)	1 (base)
Sex				
Male	1.42 (0.97–2.07)	1.21 (0.76–1.96)	1.22 (0.70–2.13)	1.18 (0.67–2.08)
Female	1 (base)	1 (base)	1 (base)	1 (base)
Age at diagnosis, y				
Birth to 9	1 (base)	1 (base)	1 (base)	1 (base)
10–19	2.06 (0.69–6.22)	1.90 (0.54–6.74)	1.78 (0.40–7.95)	2.01 (0.44–9.18)
20–29	2.36 (0.80–6.95)	1.83 (0.52–6.42)	1.67 (0.38–7.38)	1.72 (0.38–7.78)
30–39	2.90 (1.01–8.35)	2.48 (0.73–8.45)	2.61 (0.61–11.1)	2.61 (0.60–11.4)
Race/ethnicity				
White	1 (base)	1 (base)	1 (base)	1 (base)
Black	1.75 (0.77–3.97)	1.82 (0.63–5.20)	2.48 (0.72–8.51)	2.37 (0.68–8.31)
Hispanic	1.79 (1.14–2.79)	2.13 (1.16–3.89)	2.20 (1.04–4.63)	2.23 (1.01–4.92)
Asian	1.3 (0.65–2.61)	1.35 (0.56–3.26)	1.11 (0.36–3.51)	1.24 (0.39–3.87)
Neighborhood SES, quintiles				
1. Lowest 20%	1.80 (0.92–3.52)	1.03 (0.44–2.44)	0/83 (0.28–2.52)	0.87 (0.27–2.80)
2.	1.91 (0.96–3.79)	1.08 (0.46–2.53)	0.99 (0.33–2.92)	1.03 (0.33–3.20)
3. Middle 20%	1.38 (0.67–2.84)	0.93 (0.39–2.23)	0.88 (0.29–2.72)	0.93 (0.29–3.01)
4.	1.30 (0.61–2.77)	0.81 (0.32–2.02)	0.79 (0.25–2.53)	0.83 (0.25–2.72)
5. Highest 20%	1 (base)	1 (base)	1 (base)	1 (base)
Initial care at hospitals affiliated with NCI-designated cancer centers				
Yes	1 (base)	1 (base)	1 (base)	1 (base)
No	1.53 (0.92–2.55)	1.07 (0.57–2.00)	1.30 (0.62–2.72)	1.19 (0.55–2.56)
Health insurance (limited to patients diagnosed between 1996–2011 [n = 609])				
None	3.91 (2.01–7.62)	NA	NA	2.67 (1.10–6.52)
Public	0.66 (0.39–1.13)	NA	NA	0.66 (0.32–1.33)
Private	1 (base)	NA	NA	1 (base)
Unknown/NOS	0.40 (0.14–1.17)	NA	N/A	0.22 (0.06–0.79)

Abbreviations: 95% CI, 95% confidence interval; ATRA, all-*trans* retinoic acid; NA, not applicable; NCI, National Cancer Institute; NOS, not otherwise specified; OR, odds ratio; OR1, unadjusted model (1988–2011); OR2, adjusted model without insurance (1988–2011); OR3, adjusted model without insurance (1996–2011); OR4, adjusted model with insurance (1996–2011); SES, socioeconomic status.
All multivariable comparisons were adjusted for chemotherapy (yes/no) and all variables in the table unless otherwise noted.

Moreover, despite the great effectiveness of ATRA and arsenic, treatment may cause severe complications that should be recognized and treated promptly, such as differentiation syndrome. Differentiation syndrome occurs in approximately 2% to 31% of patients receiving induction therapy and can mimic other severe complications, such as pulmonary hemorrhage, renal dysfunction, and heart failure.[21] Because of the abrupt presentation and potential gravity of differentiation syndrome, the preemptive use of corticosteroids has been proposed.[22] The syndrome may be promoted by delaying chemotherapy after ATRA,[23] and delaying ATRA itself for >2 days may increase the risk of fatal hemorrhage.[24] These findings confirm the importance of early diagnosis, rapid intensive treatment, and adequate supportive care.

Importantly, we found that uninsured patients had a higher risk of early death and lower survival estimates compared with those with private and public insurance, suggesting a lack of adequate access to care. The current study results are consistent with a previous report of worse survival in uninsured versus insured adolescents and young adults (AYAs).[25] Wider insurance coverage is likely to provide better outcomes for these patients. In addition, early death was higher among Hispanic patients, and survival was lower among black and Hispanic patients compared with white patients. Similar findings have been reported in children with acute lymphoblastic leukemia,[26,27] children with AML (excluding APL),[28] and adults with AML (including APL).[14] To provide effective and sustainable treatment to patients with APL, which is a severe but highly curable disease, efforts also should address the social contributors to health inequity[29] such as poverty, inadequate access to transportation, and lack of educational resources.

TABLE 3. Relation of Sociodemographic and Clinical Factors to the Hazard of Death

Factor	Death No. (%)	Unadjusted HR1 (95% CI) (1988–2011)	Adjusted HR2 (95% CI) (1988–2011)	Adjusted HR3 (95% CI) (1996–2011)	Adjusted HR4 (95% CI) (1996–2011)
Calendar period					
1988–1995 (pre-ATRA)	94 (37.3)	2.79 (2.04–3.80)	2.84 (2.06–3.91)	NA	NA
1996–2003 (earlier ATRA era)	86 (34.1)	1.39 (1.01–1.90)	1.39 (1.01–1.91)	1.43 (1.04–1.98)	1.40 (1.01–1.94)
2004–2011 (later ATRA era)	72 (28.6)	1.0 (base)	1.0 (base)	1.0 (base)	1.0 (base)
Age at diagnosis, y					
Birth to 9	14 (5.6)	1.0 (base)	1.0 (base)	1.0 (base)	1.0 (base)
10–19	52 (20.6)	1.14 (0.63–2.05)	1.07 (0.58–1.96)	1.13 (0.51–2.52)	1.20 (0.54–2.67)
20–29	60 (23.8)	1.03 (0.58–1.85)	0.99 (0.54–1.81)	0.98 (0.44–2.16)	0.96 (0.43–2.14)
30–39	126 (50.0)	1.56 (0.90–2.72)	1.43 (0.80–2.53)	1.82 (0.85–3.88)	1.83 (0.85–3.93)
Race/ethnicity					
White	73 (29.0)	1.0 (base)	1.0 (base)	1.0 (base)	1.0 (base)
Black	20 (7.9)	1.79 (1.09–2.93)	1.81 (1.08–3.03)	1.97 (0.98–3.96)	1.80 (0.89–3.62)
Hispanic	134 (53.2)	1.33 (1.00–1.77)	1.48 (1.08–2.02)	1.38 (0.90–2.12)	1.31 (0.84–2.03)
Asian	25 (9.09)	1.11 (0.70–1.75)	1.21 (0.76–1.91)	1.11 (0.58–2.12)	1.12 (0.58–2.15)
Sex					
Male	145 (57.5)	1.42 (1.11–1.83)	1.27 (0.98–1.64)	1.52 (1.10–2.11)	1.50 (1.08–2.07)
Female	107 (42.5)	1.0 (base)	1.0 (base)	1.0 (base)	1.0 (base)
Neighborhood SES, quintile					
1. Lowest 20%	75 (29.8)	1.24 (0.82–1.86)	0.90 (0.57–1.41)	1.02 (0.54–1.94)	0.98 (0.51–1.89)
2.	58 (23.0)	1.20 (0.79–1.83)	0.94 (0.60–1.46)	1.01 (0.53–1.90)	1.00 (0.53–1.90)
3. Middle 20%	52 (20.6)	1.15 (0.75–1.77)	0.93 (0.60–1.46)	0.95 (0.50–1.82)	0.94 (0.49–1.80)
4.	33 (13.1)	0.86 (0.53–1.39)	0.72 (0.44–1.18)	0.76 (0.38–1.51)	0.75 (0.37–1.49)
5. Highest 20%	34 (13.5)	1.0 (base)	1.0 (base)	1.0 (base)	1.0 (base)
Initial care at hospitals affiliated with NCI-designated cancer centers					
Yes	41 (16.3)	1.0 (base)	1.0 (base)	1.0 (base)	1.0 (base)
No	211 (83.7)	1.35 (0.97–1.88)	1.07 (0.75–1.52)	1.31 (0.83–2.06)	1.26 (0.79–1.99)
Health insurance (only patients diagnosed between 1996–2011 [n = 609])					
None	22 (13.9)	2.57 (1.59–4.14)	NA	NA	2.00 (1.20–3.31)
Public	49 (31.0)	0.91 (0.63–1.31)	NA	NA	1.00 (0.67–1.48)
Private	74 (46.)	1.0 (base)	NA	NA	1.0 (base)
Unknown/NOS	13 (8.2)	0.82 (0.46–1.48)	NA	NA	0.64 (0.35–1.17)

Abbreviations: 95% CI, 95% confidence interval; ATRA, all-*trans* retinoic acid; HR, hazard ratio; HR1, unadjusted model (1988–2011); HR2, adjusted model without insurance (1988–2011); HR3, adjusted model without insurance (1996–2011); HR4, adjusted model with insurance (1996–2011); NA, not applicable; NCI, National Cancer Institute; NOS, not otherwise specified; SES, socioeconomic status.
All multivariable comparisons were adjusted for chemotherapy (yes/no) and all variables in the table unless otherwise noted.

In general, population-based studies,[11,12] such as the current one, demonstrate a greater percentage of cases of early death compared with multiinstitutional protocols. The differing findings may reflect the exclusion of patients who died during the first week or were too ill for chemotherapy in prior studies.[30] In the current study, when we excluded deaths that occurred within 7 days, we found 30-day mortality during the ATRA era to approximate that in clinical trials.[10,31] Similarly, when we excluded patients who died within 30 days of diagnosis, 5-year survival was close to that reported in multiinstitutional trials in children and AYAs.[32,33] These observations suggest that selection bias may contribute to the differences in reported survival and early death between most clinical trials and population-based studies.

The current study had several limitations. Hospital designation was limited to the location of initial care at the reporting facility, and therefore it is possible that some patients diagnosed at one type of facility were subsequently treated at another. However, 92% of the patients in the current study received at least part of their treatment at the reporting facility, suggesting that the current study findings were not substantially influenced by this factor. We also lacked data regarding patients' risk classification at the time of diagnosis, laboratory data, and blood products administered. Although this information would likely have contributed additional important findings, disease outcomes such as early death and survival are of paramount concern. Survival is a measure of the cancer burden and the effectiveness of the health system and plays a key role in the development of health policies.[34] Our large California APL cohort allowed us to compare early death and survival across treatment eras and to investigate sociodemographic factors associated with outcomes. To our knowledge, the current study is the first population-based study to investigate the association of race/ethnicity with early death and

survival in children with APL and to consider the association of outcome with health insurance, hospital type, age, sex, treatment era, and neighborhood SES. Furthermore, unlike previous population-based studies,[11,12,19] we were able to assess 7-day mortality.

The findings of the current study indicate a true reduction in 30-day mortality among children and AYAs with APL in California, suggesting adherence to modern therapeutic strategies. However, 7-day mortality remained high, suggesting that factors other than ATRA played a role in early death. We identified subgroups of patients who were vulnerable to early death and reduced survival, including the uninsured and Hispanic patients. Black patients also experienced worse survival. To improve outcomes among young patients with APL, efforts should focus on improving access to effective treatment, mainly among uninsured patients and those of Hispanic and black race/ethnicity.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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bjh research paper

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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Summary

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 0–39 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 ($P = 0{\cdot}062$), 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 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.

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 (Wingo *et al*, 2003; Deschler & Lubbert, 2006). Although complete remission can be achieved in approximately 75–90% of patients younger than 60 years of age, approximately 35–50% of these patients experience relapse within the following 2 years (Hann *et al*, 2004; Burnett, 2005). 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 (Sekeres *et al*, 2004; Mulrooney *et al*, 2008; Byrne *et al*, 2011; Dores *et al*, 2012; Sullivan *et al*, 2013; Schultz *et al*, 2014).

Given the lack of population-based studies focusing on young patients with AML (Pulte *et al*, 2009), we aimed to

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evaluate trends in survival and early death (i.e., death occurring within 30 d of diagnosis) among patients aged 0–39 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 authorization.

We identified all patients aged 0–39 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 (Horibe *et al*, 2001; Razzouk *et al*, 2006; Walter *et al*, 2011; Gatta *et al*, 2014; Ofran & Rowe, 2014). Based on these observations, we categorized age in four groups (0–9, 10–19, 20–29, and 30–39 years). To evaluate trends in outcomes, we used three 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; Walter *et al*, 2011; Wolfson *et al*, 2012; Pulte *et al*, 2013; Patel *et al*, 2015a; Percival *et al*, 2015) 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 d 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 d.

The 5-year survival in the three 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, USA), 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 d 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 30–39 years) was increased by 70% relative to that for younger patients (aged 0–9 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 & 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 (Fig 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

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

Characteristics	Total *N* (%)	Early death *N* (%)	*P**	1-year OS (95% CI)	5-year OS (95% CI)	10-year OS‡ (95% CI)	*P*†
Total	3935 (100)	332 (8·4)		66·8 (65·3–68·3)	42·8 (41·2–44·4)	39·6 (38·0–41·3)	
Calendar period							
1988–1995	1303 (33·1)	126 (9·7)	0·0620/0·0626	59·3 (56·6–62·0)	32·9 (30·3–35·5)	30·7 (28·3–33·3)	<0·0001/<0·0001
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)		72·8 (70·3–75·1)	50·0 (47·0–52·9)	45·2 (42·5–47·9)	
Age at diagnosis, years							
0–9	964 (24·5)	55 (5·7)	<0·0001/0·0003	73·2 (70·3–75·9)	52·4 (49·1–55·6)	50·0 (46·1–52·9)	<0·0001/<0·0001
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)		61·7 (58·9–64·3)	36·2 (33·5–38·9)	32·6 (29·9–35·4)	
Median	23	27					
Race/ethnicity							
Non–Hispanic white	1607 (40·8)	131 (8·2)	0·0230	65·4 (63·0–67·7)	44·3 (41·8–46·7)	40·8 (38·2–43·3)	0·0087
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)		70·2 (65·9–74·0)	42·8 (38·3–47·3)	40·3 (35·7–44·8)	
Sex							
Male	2106 (53·5)	188 (8·9)	0·2360	66·8 (64·7–68·8)	41·8 (39·6–44·0)	39·0 (36·8–41·2)	0·3151
Female	1829 (46·5)	144 (7·9)		66·7 (64·5–68·9)	43·9 (41·6–46·3)	40·4 (38·0–42·8)	
Initial care at hospitals affiliated with NCI-designated cancer centres							
Yes	1039 (26·4)	53 (5·1)	<0·0001	72·3 (69·5–75·0)	49·4 (46·2–52·5)	46·8 (43·5–50·0)	<0·0001
No	2896 (73·6)	279 (9·6)		64·8 (63·0–66·5)	40·4 (38·6–42·3)	37·1 (35·2–39·0)	
Neighbourhood socioeconomic status (quintiles)							
Lowest 20%	986 (25·1)	108 (11·0)	0·0180/0·0178	65·1 (62·0–68·4)	42·1 (38·9–45·4)	38·8 (35·4–42·1)	0·1446/0·0338
	826 (21·0)	61 (7·9)		68·3 (65·0–71·4)	41·0 (37·5–44·5)	37·7 (34·2–41·2)	
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)	
	714 (18·1)	57 (8·0)		68·0 (64·4–71·3)	46·2 (42·4–50·0)	42·9 (39·0–46·7)	
Highest 20%	626 (15·9)	42 (6·7)		68·4 (64·6–71·9)	45·5 (41·4–49·4)	43·1 (39·0–47·1)	
Health insurance status (limited to patients diagnosed in 1996–2011, *N* = 2632)							
None	99 (3·8)	21 (21·2)	<0·0001	56·3 (45·7–65·7)	37·9 (27·7–48·0)	37·9 (27·7–48·0)	0·0045
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)		67·9 (62·1–73·0)	42·6 (36·6–48·4)	37·1 (31·1–43·2)	

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

*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).

†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.

variables were mutually adjusted (Table III), we found an increased hazard of death for older patients compared with younger patients (30–39 vs. 0–9 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 0–9 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 30–39 years, the hazard of death was substantially higher among those who received initial care at

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

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*
Calendar period						
1988–1995	1·38 (1·04–1·83)	0·0799	N/A	0·1552	N/A	0·2208
1996–2003	1·22 (0·92–1·63)		1·23 (0·92–1·64)		1·20 (0·90–1·61)	
2004–2011	1 (reference)		1 (reference)		1 (reference)	
Sex						
Male	1·11 (0·88–1·40)	0·3656	1·21 (0·91–1·62)	0·1908	1·20 (0·90–1·61)	0·2153
Female	1 (reference)		1 (reference)		1 (reference)	
Age at diagnosis, years						
0–9	1 (reference)	0·0049	1 (reference)	0·1743	1 (reference)	0·3915
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)		1·36 (0·89–2·06)		1·27 (0·84–1·94)	
Race/ethnicity						
Non-Hispanic white	1 (reference)	0·0599	1 (reference)	0·1533	1 (reference)	0·2791
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)		0·66 (0·38–1·15)		0·66 (0·38–1·14)	
Neighbourhood socioeconomic status (quintiles)						
Lowest 20%	1·57 (1·05–2·34)	0·0934	1·58 (0·90–2·76)	0·4512	1·54 (0·87–2·72)	0·4411
	1·04 (0·68–1·57)		1·29 (0·73–2·27)		1·28 (0·72–2·26)	
Middle 20%	1·18 (0·78–1·77)		1·51 (0·86–1·73)		1·53 (0·87–2·69)	
	1·19 (0·78–1·81)		1·54 (0·87–2·70)		1·58 (0·90–2·80)	
Highest 20%	1 (reference)		1 (reference)		1 (reference)	
Initial care at hospitals affiliated with NCI-designated cancer centres						
Yes	1 (reference)	0·0002	1 (reference)	0·0004	1 (reference)	0·0004
No	1·75 (1·28–2·39)		1·96 (1·32–2·92)		1·99 (1·33–2·97)	
Health insurance status (limited to patients diagnosed in 1996–2011, *N* = 2632)						
Uninsured	N/A		N/A		2·91 (1·65–5·12)	0·0046
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)	

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 with insurance (1996–2011).
*Likelihood ratio test.

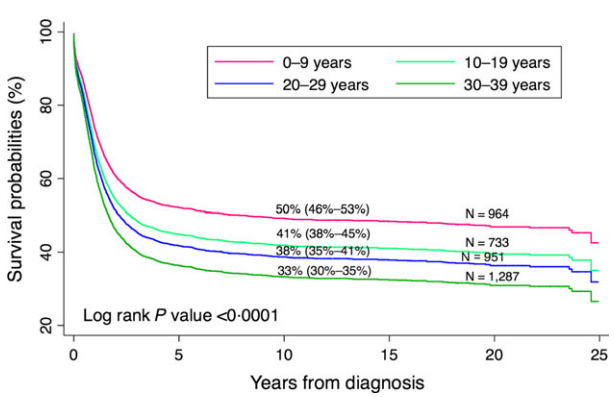

Fig 1. Overall survival after acute myeloid leukaemia by age group at diagnosis, in California, 1988–2011 (percentages in the graph correspond to 10-year survival).

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 20–29 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

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

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*
Calendar period						
1988–1995	1·58 (1·43–1·76)	<0·0001	N/A	0·0211	N/A	0·0460
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)		1·0 (reference		1·0 (reference)	
Age at diagnosis, years						
0–9	1·0 (reference)	<0·0001	1·0 (reference)	<0·0001	1·0 (reference)	<0·0001
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)		1·49 (1·28–1·74)		1·49 (1·28–1·74)	
Race/ethnicity						
Non-Hispanic white	1·0 (reference)	0·0318	1·0 (reference)	0·0505	1·0 (reference)	0·0629
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)		1·00 (0·83–1·18)		1·00 (0·84–1·19)	
Sex						
Male	1·03 (0·95–1·12)	0·4806	0·99 (0·89–1·10)	0·8900	0·99 (0·89–1·10)	0·8349
Female	1·0 (reference)		1·0 (reference		1·0 (reference)	
Neighbourhood socioeconomic status (quintiles)						
Lowest 20%	1·14 (0·99–1·31)	0·1868	1·23 (1·01–1·49)	0·0490	1·22 (1·00–1·48)	0·0453
	1·10 (0·95–1·27)		1·20 (1·00–1·46)		1·20 (0·99–1·45)	
Middle 20%	1·13 (0·98–1·30)		1·30 (1·08–1·58)		1·31 (1·08–1·59)	
	1·01 (0·87–1·15)		1·07 (0·88–1·30)		1·07 (0·88–1·31)	
Highest 20%	1·0 (reference)		1·0 (reference		1·0 (reference)	
Initial care at hospitals affiliated with NCI-designated cancer centres						
Yes	1·0 (reference)	0·0009	1·0 (reference	0·0004	1·0 (reference)	0·0002
No	1·18 (1·07–1·31)		1·26 (1·11–1·43)		1·27 (1·11–1·45)	
Health insurance status (limited to patients diagnosed in 1996–2011, $N = 2632$)						
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	N/A	1·27 (1·07–1·51)	0·0204

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.

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) (Sekeres *et al*, 2004; Aplenc *et al*, 2006; Rubnitz *et al*, 2007; Bradley *et al*, 2011; Byrne *et al*, 2011; Dores *et al*, 2012; Pulte *et al*, 2012, 2013; Patel *et al*, 2015b). 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 (Sekeres *et al*, 2004; Rubnitz *et al*, 2007). 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 two consecutive clinical trials

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

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*
Calendar period								
1988–1995	1·84 (1·45–2·34)	<0·0001	1·52 (1·19–1·93)	0·0034	1·29 (1·05–1·59)	0·0049	1·71 (1·44–2·04)	<0·0001
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)		1·0 (reference)		1·0 (reference)		1·0 (reference)	
Race/ethnicity								
Non-Hispanic white	1·0 (reference)	0·2468	1·0 (reference)	0·7294	1·0 (reference)	0·0122	1·0 (reference)	0·0821
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)		1·16 (0·84–1·60)		1·28 (0·99–1·64)		0·84 (0·67–1·05)	
Sex								
Male	0·93 (0·77–1·12)	0·4455	0·89 (0·73–1·08)	0·2287	1·17 (0·99–1·38)	0·0734	1·06 (0·92–1·21)	0·4152
Female	1·0 (reference)		1·0 (reference)		1·0 (reference)		1·0 (reference)	
Neighbourhood socioeconomic status (quintiles)								
Lowest 20%	0·88 (0·63–1·22)	0·4063	1·11 (0·80–1·53)	0·4579	1·26 (0·94–1·68)	0·0583	1·19 (0·94–1·51)	0·1260
	1·07 (0·77–1·47)		0·96 (0·69–1·32)		1·03 (0·77–1·38)		1·21 (0·96–1·53)	
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)	
	0·83 (0·59–1·17)		0·82 (0·58–1·16)		0·84 (0·62–1·14)		1·31 (1·04–1·64)	
Highest 20%	1·0 (reference)		1·0 (reference)		1·0 (reference)		1·0 (reference)	
Initial care at hospitals affiliated with NCI-designated cancer centres								
Yes	1·0 (reference)	0·3314	1·0 (reference)	0·0220	1·0 (reference)	0·3310	1·0 (reference)	0·0042
No	1·10 (0·91–1·32)		1·29 (1·03–1·61)		1·11 (0·90–1·37)		1·31 (1·08–1·58)	

HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; NCI, National Cancer Institute.
*Likelihood ratio test.

by the Children's Oncology Group (patients aged 0–21 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 (Goggins & Lo, 2012; Lim *et al*, 2014; Pulte *et al*, 2013; Abrahão *et al*, 2015b), 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 0–9 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 30–39 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 & 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 & 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

Table V. 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.

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*
Calendar period								
1996–2003	1·31 (1·02–1·68)	0·0308	1·28 (0·99–1·64)	0·0580	0·92 (0·74–1·15)	0·4640	1·13 (0·94–1·36)	0·2000
2004–2011	1·0 (reference)		1·0 (reference)		1·0 (reference)		1·0 (reference)	
Race/ethnicity								
Non-Hispanic white	1·0 (reference)	0·0821	1·0 (reference)	0·8872	1·0 (reference)	0·0392	1·0 (reference)	0·4981
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)		1·01 (0·66–1·55)		1·40 (1·01–1·92)		0·83 (0·62–1·11)	
Sex								
Male	0·89 (0·70–1·12)	0·3220	0·84 (0·65–1·08)	0·1688	1·08 (0·86–1·35)	0·5054	1·06 (0·88–1·27)	0·5343
Female	1·0 (reference)		1·0 (reference)		1·0 (reference)		1·0 (reference)	
Neighbourhood socioeconomic status (quintiles)								
Lowest 20%	0·92 (0·59–1·43)	0·6758	1·12 (0·71–0·78)	0·7838	1·37 (0·92–2·04)	0·0281	1·34 (0·95–1·88)	0·0035
	1·16 (0·76–1·77)		0·92 (0·59–1·44)		1·03 (0·69–1·53)		1·56 (1·14–2·15)	
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)	
	0·92 (0·59–1·45)		0·87 (0·54–1·40)		0·77 (0·51–1·16)		1·60 (1·17–2·20)	
Highest 20%	1·0 (reference)		1·0 (reference)		1·0 (reference)		1·0 (reference)	
Initial care at hospitals affiliated with NCI-designated cancer centres								
Yes	1·0 (reference)	0·3512	1·0 (reference)	0·0078	1·0 (reference)	0·1414	1·0 (reference)	0·0095
No	1·12 (0·88–1·43)		1·44 (1·09–1·90)		1·24 (0·93–1·66)		1·39 (1·08–1·80)	
Health insurance status								
None	1·60 (0·63–4·02)	0·4384	1·78 (0·85–3·75)	0·2399	0·94 (0·57–1·55)	0·1965	1·78 (1·14–2·76)	0·0986
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)		1·35 (0·92–1·99)		1·45 (1·02–2·07)		1·17 (0·86–1·59)	

HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; NCI, National Cancer Institute.
*Likelihood ratio test.

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 & 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 & 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 & Schiffer,

2013). Although improvements in HSCT have led to a significant decrease in transplant-related morbidity and mortality in patients with AML (Ferrara & 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 & 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 & Janne, 2015)] and big data infrastructure (including access to electronic medical records and linkage of cancer registry data with insurance claims information) (Meyer & 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 & 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 1–5 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 10–39 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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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.

Conflict of interest

The authors declare no conflict of interests.

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Disparities found to affect survival for older children, adolescents and young adults with acute myeloid leukemia

New study from the Cancer Prevention Institute of California finds lower survival rate for blacks and those treated at centers not affiliated with the National Cancer Institute.

FREMONT, CA (PRWEB) FEBRUARY 18, 2016

Acute leukemia is the leading cause of cancer death among patients 39 years of age and younger. Without treatment, most patients die within months, if not weeks, of diagnosis. The five-year survival was only about 50% for the most recent treatment period of 2004 – 2011.

In a study led by the Cancer Prevention Institute of California(CPIC) and the London School of Hygiene and Tropical Medicine, and published in the February issue of the British Journal of Hematology, researchers analyzed 3,935 patients with acute myeloid leukemia (AML) up to 39 years of age in California from 1988 – 2011.

For this study researchers used data from the California Cancer Registry, which participates in the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI). To the authors' knowledge, this is the first population-based study that simultaneously examined the influence of race/ethnicity, neighborhood socioeconomic status, type of health insurance and treatment facility on survival.

Renata Abrahão MD, MSc

"Our study reveals that survival inequalities persist among vulnerable

Researchers found several subgroups of patients with worse survival. They tended to fall into one of these groups:

- age group (10 – 39 years)
- lower neighborhood socioeconomic status
- black race/ethnicity
- receipt of initial care in hospitals not affiliated with the NCI
- lack of health insurance

patients with acute myeloid leukemia such as the uninsured, those of black race/ethnicity and adolescents and young adults." said Renata Abrahão MD, MSc.

The diagnosis of AML in older children, adolescents and young adults may require more intensive treatment, which may lead to a higher probability of treatment-related complications. Older children, adolescents and young adults are also less likely to participate in clinical trials and more likely to receive treatment at hospitals not affiliated with the NCI in comparison to younger children.

A significant association was found between lower socioeconomic neighborhoods and early death suggesting that these patients lacked access to optimal treatments during the critical days after initial diagnosis.

It is not clear what factors accounted for the disparities in survival among black patients. Researchers speculate that genetics may contribute to the difference in chemotherapy response or that black patients had less access to chemotherapy and other treatments such as hematopoietic stem cell transplantation.

Recent studies have also shown the biology of pediatric AML differs from adult AML which may lead to a favorable prognosis in younger patients.

Researchers also found evidence of increased early death and lower survival among uninsured patients compared to privately or publicly insured patients. Health insurance information was available in the California Cancer Registry for patients diagnosed from 1996 – 2011.

"Our study reveals that survival inequalities persist among vulnerable patients with acute myeloid leukemia such as the uninsured, those of black race/ethnicity and adolescents and young adults." said Renata Abrahão MD, MSc, a visiting research scientist at CPIC and lead author of the study. "This study can serve as a baseline to compare changes in survival that may result from potential improvements in health insurance coverage following the implementation of the Affordable Care Act (Obamacare)."

"Moreover, this study showed that survival after AML remains low among young patients and highlights the need for new therapeutic regimens to treat this disease with various subtypes. We emphasized the importance of linking population-based data with genetic and clinical information contained in the patients' medical records in order to better understand the causes of survival inequalities."

The work was supported by Children with Cancer UK.

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About the Cancer Prevention Institute of California
The Cancer Prevention Institute of California is the nation's premier organization dedicated to preventing cancer and to reducing its burden where it cannot yet be prevented. CPIC tracks patterns of cancer throughout the entire population and identifies those at risk for developing cancer. Its research scientists are leaders in investigating the causes of cancer in large populations to advance the development of prevention-focused interventions. CPIC's innovative cancer prevention research and education programs, together with the work of the Stanford Cancer Institute, can make our vision of a world without cancer a reality. For more information, visit CPIC's official website at http://www.cpic.org.

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