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Authors
Zhang, L
Samad, A
Pombo-de-Oliveira, MS
et al.

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Global Characteristics of Childhood Acute Promyelocytic Leukemia

L Zhang[1,*], **A Samad**[1,*], **MS Pombo-de-Oliveira**[2], **G Scelo**[3], **MT Smith**[1], **J Feusner**[4], **JL Wiemels**[5], and **C Metayer**[1]

[1]School of Public Health, University of California, Berkeley, USA

[2]Pediatric Hematology-Oncology Program, Research Center-National Institute of Cancer, Rio de Janeiro, Brazil

International Agency for Research on Cancer (IARC), Lyon, France

[4]Department of Hematology, Children's Hospital and Research Center Oakland, Oakland, USA

[5]Department of Epidemiology and Biostatistics, University of California, San Francisco, USA

Abstract

Acute promyelocytic leukemia (APL) comprises approximately 5–10% of childhood acute myeloid leukemia (AML) cases in the US. While variation in this percentage among other populations was noted previously, global patterns of childhood APL have not been thoroughly characterized. In this comprehensive review of childhood APL, we examined its geographic

Corresponding Author: Luoping Zhang, Ph.D., Genes and Environment Laboratory, Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, 388 Li-Ka Shing Center, Berkeley, CA 94720, USA, Telephone: +1 (510) 643-5189 | Fax: +1 (510) 642-0427 | luoping@berkeley.edu.

*These authors contributed equally to this work

Aaida Samad, B.A., Genes and Environment Laboratory, Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, 388 Li-Ka Shing Center, Berkeley, CA 94720, USA, Telephone: +1 (510) 643-5189 | Fax: +1 (510) 642-0427 | aaida.samad@gmail.com

Maria S. Pombo-de-Oliveira, M.D., Ph.D., Pediatric Hematology-Oncology Program Research Center-Instituto Nacional de Câncer, Rua André Cavalcanti, 37; 6º andar, CEP 20231050-Rio de Janeiro, Brazil, Telephone: +55 21 32076532 | Fax: +55 21 32076566 | mpombo@inca.gov.br

Ghislaine Scelo, Ph.D., International Agency for Research on Cancer (IARC), 150 cours Albert Thomas, 69008 Lyon, France, Telephone: +33 4 7273 8173 | Fax: +33 4 7273 8342| scelog@iarc.fr

Martyn T. Smith, Ph.D., Professor & Director, Berkeley Institute of the Environment and Superfund Research Program, Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, 386 Li Ka-Shing Center, Berkeley, CA 94720-3370, USA, Telephone: + 1 (510) 642-8770 | Fax: +1 (510) 642-0427 | martynts@berkeley.edu

James Feusner, M.D., Children's Hospital Oakland, 747 52nd Street, Oakland, CA, 94609, USA, Telephone: +1 (510) 428-3689 | Fax: +1 (510) 601-3916 | jfeusner@mail.cho.org

Joseph Wiemels, Ph.D., Department of Epidemiology and Biostatistics, University of California, San Francisco, 1450 3rd Street, San Francisco, CA 94158, USA, Telephone: +1 (415) 514-0577 | Fax: + 1 (415) 502-7411 | joe.wiemels@ucsf.edu

Catherine Metayer, M.D., Ph.D., Associate Adjunct Professor, School of Public Health, University of California, Berkeley, 1995 University Avenue, Suite 460, Berkeley, CA 94704-7392, USA, Phone: +1 (510) 643-1156 | Fax: +1 (510) 642-9319 | cmetayer@berkeley.edu

CONFLICT OF INTEREST

Dr. Smith has received consulting and expert testimony fees from lawyers representing both plaintiffs and defendants in cases involving claims related to exposure to chemicals and leukemia. The remaining authors declare that there are no conflicts of interest.

pattern and the potential contribution of environmental factors to observed variation. In 142 studies (spanning >60 countries) identified, variation was apparent—*de novo* APL represented from 2% (Switzerland) to >50% (Nicaragua) of childhood AML in different geographic regions. Because a limited number of previous studies addressed specific environmental exposures that potentially underlie childhood APL development, we gathered 28 childhood cases of therapy-related APL, which exemplified associations between prior exposures to chemotherapeutic drugs/radiation and APL diagnosis. Future population-based studies examining childhood APL patterns and the potential association with specific environmental exposures and other risk factors are needed.

Keywords

acute promyelocytic leukemia; AML-M3; pediatric leukemia; therapy-related leukemia; environmental exposure; risk factors

INTRODUCTION

Leukemia is the most common type of cancer in children

Leukemia, the most common type of cancer in children [1], accounts for 25–35% of cases of childhood cancer in most populations [1, 2]. Acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) comprise the two major subtypes of childhood leukemia, with ALL accounting for 76% of childhood leukemia cases [3, 4]. AML, the second largest subgroup in children but the most common leukemia type among adults [3], represents 15–20% of leukemia cases in children, and is responsible for up to 30% of pediatric leukemia related deaths [4, 5].

De novo acute promyelocytic leukemia (APL), a subtype of AML, represents about 5–10% of childhood AML cases in the United States [6]. Previous studies, in which the majority of cases were reported from clinical trials or treatment protocols, rather than population-based analyses, have suggested that in certain Latin American, European and African populations, APL comprises relatively higher percentages of childhood AML [7]. However, variation in incidence among geographic regions has not been formally explored at a global level.

This review not only provides an overview of childhood APL, but also aims to: 1) examine childhood APL as a proportion of AML in countries around the world in order to gain insight into potential global geographic patterns; 2) analyze whether a previously hypothesized gender predominance in childhood APL cases exists; and, 3) discuss the potential contribution of environmental risk factors to the development of APL, using the example of exposure to previous therapy for primary diseases.

APL is a relatively well-characterized subtype of AML

AML encompasses a heterogeneous group of leukemias characterized by increased proliferation of myeloid cells in the bone marrow [8]. Among the subtypes of AML, APL is of particular interest due to its well-characterized etiology. With targeted treatment involving chemotherapy and all-trans retinoic acid (ATRA), the survival rate of APL in

children is relatively high (75–80%) [9]. Additionally, variation in the incidence of APL as a percentage of total childhood AML across certain racial/ethnic groups and geographic regions has been previously observed, and is potentially attributable to certain environmental exposures.

The etiology, molecular mechanisms, and treatment of APL have been comprehensively studied. In 1990, based on the observation that retinoic acid, a vitamin A derivative, is able to induce *in vivo* differentiation of APL cells into mature granulocytes, a French team of researchers examined the retinoic acid receptor gene (*RARα*) and discovered that the t(15;17) translocation, characteristic of the majority of APL cases, involved the *RARα* gene (located on chromosome 17) and the *PML* locus on chromosome 15, resulting in *PML/RARα* fusion products [10, 11].

APL classification is based on morphological and cytogenetic information

Under the French-American-British (FAB) classification system, AML is categorized into eight subtypes (AML-M0 to M7) based on morphological features, as well as percentage and maturation of myeloblasts [12]. Under the FAB system, APL is characterized as subtype AML-M3, in which the predominant cells are promyelocytes with heavy granules and Auer rods. Diagnosing the microgranular variant of APL (AML-M3v) can be difficult because its morphological and cytochemical features are often non-specific, leading to misdiagnosis as AML-M4 or AML-M5 [13]. For these reasons, APL diagnosis by morphology alone has its limitations.

Random somatic chromosomal abnormalities resulting in fusion gene rearrangements are common in the malignant cells of patients with AML. About 95% of APL cases are characterized by recurrent chromosomal rearrangements of the *RARα* gene located on chromosome 17 [14], with the majority involved in a t(15;17)(q24;q21) translocation where the *RARα* gene fuses to the *PML* gene on chromosome 15. Eight rare partner genes (in addition to *PML*) which fuse to *RARα* have been previously described: *NPM1*, *NUMA1*, *PLZF*, *PRKAR1A*, *FIP1L1*, *BCOR*, *STAT5B* and a yet unidentified gene. These are represented by cytogenetic abnormalities t(5;17)(q35;q21), t(11;17)(q13;q21), t(11;17)(q23;q21), del(17)(q21;q24)/t(17;17)(q21;q24), t(4;17)(q12;q21), t(X;17)(p11;q12), der(17) and t(3;17)(p25;q21), respectively [15–22].

Recently, the AML committee of the International BFM Study Group published guidelines for the diagnosis and management of AML in children and adolescents with recommendations that cytogenetic and molecular methods should be performed in order to stratify AML subgroups by risk [23]. The advent of cytogenetic analysis has allowed the identification and categorization of recurring chromosomal aberrations associated with some AML subtypes, leading to the World Health Organization (WHO) classification system [24, 25]. Under the WHO classification system [26], AML subtypes are defined using more comprehensive information sources, including genetic, immunophenotypic, biological and clinical features, rather than morphology alone [27]. Under this system, APL (ICD-10 C92.4) falls into a category of myeloid leukemia with recurrent genetic abnormalities [28].

Variation in the geographic distribution of childhood APL may involve genetic and environmental factors

A notable epidemiologic feature of pediatric APL is that observed incidence rates, based on data from hospital-based registries and clinical trials, differ markedly among certain ethnic groups and geographic regions [14, 29]. Previous studies reported a high frequency of APL in certain Latin American, European and African populations, accounting for 17–58% of pediatric AML cases and 22–37% of adult AML cases [7]. APL incidence in studies like these traditionally has been estimated based on its relative frequency among other AML subtypes in large clinical trials because population-based registries did not distinguish APL from other AML subtypes until recently, and as a result, the true incidence rate of APL is nearly unknown [29].

The geographic variation in relative frequency of childhood APL potentially suggests that genetic predisposition towards APL and/or environmental exposures to specific risk factors may be involved [14]. Genetic predisposition may influence susceptibility to breakage at the site involved in chromosomal translocations, such as t(15;17), in APL [7]. In addition, nutritional and environmental factors [30], obesity at diagnosis [31], as well as dietary or metabolic patterns of ingested vitamin A (or its derivatives) [7, 32] have suggested associations with APL. Besides suggested genetic and environmental factors, exposure to chemotherapeutic drugs and other toxins may also contribute to APL development.

Therapy-related childhood APL can occur following treatment for a primary malignancy

Development of therapy-related AML (t-AML) and APL (t-APL) is a potential long-term complication of exposure to high doses of chemotherapy and/or radiation involved in treatment of primary diseases, and leukemia that arises following exposure to chemotherapy is primarily AML [33]. Previous studies have suggested that radiation and chemotherapy with alkylating agents and topoisomerase II inhibitors are potentially implicated in the development of t-APL specifically [34–36]. In recent years, the development of t-AMLs have been a cause of increasing concern due to the increase in the number of individuals surviving primary malignancies [37]. Under the WHO classification of AML (ICD-10 C92.0), t-AMLs following chemotherapy are considered to be distinct diagnostic entities [38], and the system recognizes two types of t-AML based on causative therapy: alkylating agent/radiation–related and a topoisomerase II inhibitor–related types [27]. Similar to therapy-related leukemias with *MLL* translocations, t-APL following treatment with topoisomerase II inhibitors has distinct breakpoints at chromosomal translocations involving the *RARα* gene, which appear to be caused by the drug-topoisomerase '*cleavable complexes*' [39, 40]. Such breakpoint features are a direct link between a causal exposure and leukemia, which hopefully could be extended to *de novo* or idiopathic APL in the future.

Environmental exposures are implicated in APL and AML development

Other than exposure to radiation and drugs associated with therapy for a primary disease, AML development has also been associated with a variety of different environmental risk factors in both adults and children. In adults, an increased risk of AML has been strongly associated with exposure to ionizing radiation and benzene [41]. Additionally, exposures to other toxic chemicals and occupational hazards have been associated with AML in adults

[3]. Due to the relative rarity of childhood AML and APL, fewer epidemiological studies addressing environmental exposure have been conducted [41]. Childhood exposure to petroleum solvents [42], as well as *in utero* exposure to ionizing radiation [43], and parental smoking [44], are a few among a range of risk factors reported as being potentially associated with development of childhood AML. In a recent case-control study of California children, Heck *et al* examined associations between air toxics exposures in pregnancy and early life in relation to leukemia in young children, and found that risk of AML was increased with 3rd trimester exposures to chloroform, benzene, and two other traffic-related chemicals (meta/para-xylene and toluene) [45]. There appear to be a limited number of studies that have previously examined childhood exposure and the development of childhood APL specifically.

Relevance of examining the geographic pattern of childhood APL

In this review, we aim to examine regional variation in the global geographic pattern of childhood APL. If the variation exists, it could potentially reflect the involvement of genetic, cultural, and environmental exposure related factors. Therefore, comprehensive characterization of such variation could help with the design of studies to examine the contribution of these factors. Data on childhood APL incidence is lacking for many global regions, however. Ribeiro and Rego have reported previously that a lack of population-based registries in developing countries makes determining the true frequency of APL difficult [29]. Recently, a population-based study of childhood leukemia in Brazil demonstrated that substantial regional differences in the incidence of AML; this finding, which corroborates hospital-based data described previously, warrants further ecological study [46]. Because the vast majority of the published data in APL came from clinical and/or descriptive epidemiologic data, the real incidence rate of APL is still unknown even in well-developed countries.

In the current study, we measured the frequency of childhood APL cases as a percentage of childhood AML, based on data from hospital-, study- or registry-based populations around the world. We sought to examine geographic variation and potential contributions, and to highlight regions of the world where data are not available so further studies including these areas can be conducted to increase the scope of the current understanding of this disease.

MATERIALS AND METHODS

Study Selection and Criteria

Broad literature searches were conducted from June 2011 to February 2014 using PubMed and Google Scholar databases to locate original, peer-reviewed research and review articles related to childhood AML, APL, t-APL, geographic distributions, potential risk factors. Initially, combinations of relevant key words were used to search for relevant studies, and terms used included: *acute myeloid leukemia (leukaemia), pediatric (paediatric) acute promyelocytic leukemia*, *childhood leukemia*, *incidence rate*, and *exposure* (Figure 1). Following this initial search, we systematically searched for studies across six continents by using a combination of specific country names with the phrases “acute myeloid leukemia”, “acute promyelocytic leukemia” and/or “childhood leukemia.” Cross-referencing citations of

all relevant articles, searching for frequently recurring author names, and searching for ongoing leukemia clinical trials also identified additional studies.

Inclusion criteria—To be included, relevant studies had to contain information regarding a series of leukemia cases in a hospital or registry-based population where the number of cases of both childhood AML and APL were available. If multiple publications reported overlapping data from the same group of subjects, only the study with most recent and complete data was included. Information from the abstracts of relevant studies for which the full text was unobtainable was abstracted when possible. Studies in languages other than English were included if they were readily translatable by coauthors (written in Spanish or Chinese), or if they had a sufficiently informative English abstracts.

Exclusion criteria—Reviews (if all the original studies relevant to APL cited in the review were available to us), studies without APL data, and studies published in languages other than English, Spanish and Chinese that were not readily translatable, were excluded. In additions, studies for which full text publications were unobtainable were excluded if the abstract did not contain sufficient information.

Characteristics of the of Final Studies Included

After examining approximately 550 gathered publications, a total of 228 studies met the criteria for inclusion (Figure 1, Table 1). Of these, 142 studies [2, 5, 7, 24, 30, 41, 47–182] provided information on both childhood *de novo* APL and AML, and 24 studies [29, 183–205] examined *de novo* childhood APL only. To examine gender, the *de novo* childhood APL studies were divided into two groups: AML studies with APL data and APL only studies (Table 1, Supplementary Tables S1a–b). In total, 52 studies provided information about therapy-related APL, with 30 studies examining t-APL [36, 37, 206–233] in children and 26 studies examining t-APL in adults [38, 40, 208, 214, 216, 220, 234–253]. Four studies [208, 214, 216, 220] contained information about both children and adults. In addition, 10 studies [254–263] that discussed environmental and occupational related risk factors for APL in adults were included.

Data Abstraction and Calculations

From these 142 studies, all relevant data were abstracted regarding the number of cases of AML and APL, the region where the study was conducted, the years during which the data were collected, age at diagnosis, gender, and the method(s) of APL classification when available. However, the criteria for defining childhood leukemia varied widely among these studies (see details in Table 2a–f) *e.g.* the age of children was defined as ≤ 14, ≤ 18, and ≤ 21 years old.

The percentage of childhood AML cases that APL cases comprise was calculated for each study (Table 2a–f). To clearly visualize the data from Table 2a–f, we present data from the 61 countries, or regions spanning multiple countries, in a global map (Figure 2). For each country, childhood APL as a percentage of total AML, averaged across all studies from that country (Table 2a–f), was classified into one of 5 categories: <5%, 5–10%, 10–15%, 15–20%, and >20% (right end point included). These categories are color-coded in Figure 2.

The colored dots representing the summary APL statistic for each country are scaled to indicate the number of studies included. Multinational studies that spanned large, non-contiguous geographic areas (noted in Table 2f) were excluded from Figure 2. Averaging across studies to represent entire countries in Figure 2, particularly larger countries like China, Russia and the United States, may mask sub-regional variation in APL prevalence. Therefore, when available, data regarding specific regions or cities was also listed in Table 2a–f. In addition, the source of cases (case series, case-control studies, clinical trials or cancer registries) was noted. For t-APL in children, information regarding the primary malignancy, treatment for primary malignancy, time to APL (latency), karyotype, gender and age at t-APL diagnosis, and outcome were also collected (Supplementary Table S2).

Assessment Method for Association Tests

Using the information shown in Table 2, we fit a logistic regression on grouped data to assess the association between the proportion of APL among AML cases with geographical location (continents defined as North America; South/Central America; Europe; Africa; Asia; Oceania), source of cases (case series; clinical trials; case-control studies; cancer registries), period of data collection (median of recruitment time window, in categories following quartile distribution: 1969–87; 1988–95; 1996–2001; 2002–11), eligible age categories (0–2; 0–12; 0–15; 0–19; 0–21), and eligibility of secondary/therapy-related leukemia (no; unknown).

RESULTS & DISCUSSION

Global pattern of childhood APL as a percentage of AML

Geographic area—The 142 studies included in the current review that had relevant data on *de novo* APL and AML cases represented 61 individual countries or regions spanning multiple countries (Table 2, Figure 2). Information regarding the numbers of childhood AML and APL cases was available for countries in North America (Table 2a), South and Central America (Table 2b), Europe (Table 2c), Africa and the Middle East (Table 2d), Asia (Table 2e), and Oceania (Table 2f). The available data were mostly from Western Europe, South America and Asia. Information regarding numbers of APL cases in Eastern Europe, Southeast Asia, the Middle East and large geographic areas of Africa was more limited. Only six countries in Africa and six countries in the Middle East were represented in the gathered studies.

Table 2 shows that the ratios of *de novo* APL to total childhood AML cases, calculated for individual studies. Ratios for individual studies were wide ranging, representing from 0% to greater than 50% of AML cases. Figure 2 presents APL as a percentage of total AML, averaged across all studies from that country. In North America, for example, the average ratio of APL to AML is 6.2% in the United States and the rates were around 16% in Canada and Mexico (Table 2a). The lowest proportions of APL (where APL comprised less than 5% of AML cases, colored in blue) were reported in Saudi Arabia and five European countries (Austria, Germany, Netherlands, Sweden, and Switzerland), with the lowest rate of 2.4% in Switzerland (Table 2c). Certain European countries like Italy, the Czech Republic, Belarus and Spain featured relatively higher proportions of APL compared to the rest of Europe. The

highest proportions of APL (where APL represented greater than 20% of AML cases, colored in red) were reported in seven countries: Iraq, Pakistan, Italy, Cuba, Nicaragua, Guatemala, and Venezuela, with the highest rate of 58.8% in Nicaragua (Table 2b).

Besides the highest proportions (>20%) of APL in South and Central America referenced above, Brazil and Argentina featured 15–20% of AML cases (Table 2b, Figure 2). APL comprised 10–15% of AML cases in the remaining four studies we gathered from South and Central America, which included patients from Costa Rica, Chile, Bolivia (Table 2b) and a larger multinational region that encompassed Guatemala, Honduras and El Salvador (Table 2f). In the six African countries for which data were available (Table 2d, Figure 2), proportions of APL were varied: APL represented around 15–20% of pediatric AML cases in 4 countries (Nigeria, South Africa, Tunisia, and Sudan), 10–15% of AML cases in Egypt and 5–10% of AML cases in Malawi. Proportions of APL were similarly variable in the Middle East, ranging from as low as 3.4% of AML cases in Saudi Arabia and to as high as 34.5% of AML cases in Iraq (Table 2d, Figure 2). In East Asia, Mainland China featured a relatively higher percentage of APL (19.3%) when compared to the rest of the region (Table 2e, Figure 2), while the highest rate in Asia (~25%) was in Pakistan.

Assessment of the association—A total of 115 studies were included in the regression while 27 studies were excluded due to missing information for one or several variables under analysis. All variables in the model were significantly associated with the proportion of APL: continent ($p < 0.0001$); source of cases ($p < 0.0001$), period of data collection ($p < 0.0001$); eligible age group ($p < 0.0001$); and eligibility of secondary/therapy-related leukemias ($p < 0.0001$). Risk estimates for continent adjusted for other variables in the model indicated that, compared to North America, the proportion of APL among AML was two times higher in South/Central America (odds ratio (OR)=2.01, 95% confidence interval (CI)=1.49–2.71) and Oceania (OR=2.07, 95%CI 1.37–3.12), and approximately 50% higher in Africa (OR=1.52, 95%CI 1.06–2.17). Differences were moderate and non-significant between North America and other geographical locations: Europe (OR=1.12, 95%CI 0.88–1.44), Middle East (OR=1.01, 95% CI 0.68–1.50), and Asia (OR=1.10, 95%CI 0.83–1.46).

We also tested all possible combinations of interaction terms in the model. The interaction was significant ($p < 0.05$) between continent and data collection period, age, and source of cases. Source of cases interacted with data collection period, age, and inclusion of secondary/therapy-related leukemias. Period of recruitment also interacted with source of cases and age. The main effect of continent only remained significant ($p < 0.0001$) after adjustment for these interaction terms.

Repeating this analysis after exclusion of studies where eligibility of secondary/therapy-related leukemias was not clearly stated (unknown), a total of 76 studies were included in the regression while 10 studies were excluded due to missing information for one or several variables under analysis. All variables in the model were significantly associated with the proportion of APL: continent ($p < 0.0001$); source of cases ($p < 0.0001$), period of data collection ($p = 0.0069$); and eligible age group ($p = 0.0057$). Risk estimates for continent adjusted for other variables in the model indicated that, compared to North America, the proportion of APL among AML was more than two times higher in South/Central America

(OR=2.43, 95% CI=1.70–3.47) and Oceania (OR=2.28, 95%CI 1.48–3.51. Differences were moderate between North America and other geographical locations: Europe (OR=1.32, 95%CI 0.99–1.77), Africa (OR=1.35, 95% CI 0.81–2.28), Asia (OR=1.40, 95%CI 0.99–1.98), and Middle East (OR=0.73, 95%CI 0.35–1.53).

We also tested all possible combinations of interaction terms in this more restricted model. The interaction was significant ($p < 0.05$) between continent and period, continent and source of cases, period and source of cases, and period and age. Main effect of continent ($p < 0.0001$), source of cases ($p = 0.0115$), and period ($p < 0.0001$) remained significant after adjustment for these interaction terms.

Data source—A few previous studies using hospital-based data examined the incidence of childhood APL in Northern Italy, Mexico City and El Salvador [59, 86], as well as childhood APL as a proportion of AML [29]. However, these studies examined APL data on a regional scale. In this review we combined information from 142 studies, providing a global view of APL as a proportion of AML. The information abstracted from studies included in this review was based largely on hospital- and study-based populations rather than registries. In total, only 12 studies had data from local or national registries [2, 70, 83, 87, 98, 105, 107, 124, 142, 168, 169, 171]. Out of the remaining 130 studies, 11 hospital-based studies [59, 64–66, 102, 118, 119, 150, 174, 182, 198] had data that were more representative of the population, as the hospitals where patients were treated were either the only referral centers, or the major referral centers, for pediatric leukemia in the region or country. For some countries, information was available from both hospital- and study-based populations as well as registries, allowing us to directly compare calculated ratios of APL to AML. For example, 9 Japanese studies [143–151] were hospital-based and their average proportion of childhood APL among AML was 9.13%, while one recently published study from a Japanese registry [142] reported that childhood APL represented 7.9% of total AML. However for many studies, information regarding regional variation was limited. In some countries for which more than one study was available, we observed that there was often variation between studies regarding the percentage of total AML cases that APL comprised. For example, in Mainland China, APL ranged from 5.3% to 36.2% of AML cases (Table 2e).

Data collection period and APL classification method—The studies included covered a wide range of publication years, with the earliest studies published as early as 1979 and the most recent studies published in 2013 and 2014. In the studies gathered, APL was defined using cellular morphology and/or cytogenetics (based on the presence of the chromosomal translocation t(15;17) or the detection of *PML/RARα* fusion genes by PCR). Earlier studies largely used morphology combined with the presence of coagulopathy to diagnose APL, while more recent studies, or studies involving the testing of novel therapies, morphology and cytogenetics or PCR were used to confirm the presence of APL. Lack of cytogenetics and/or molecular tests in earlier studies would have potentially contributed to less counted cases due to misdiagnosed variants of APL as other AML subtypes, as described earlier.

Sample size—Ranging from as few as 11 children to more than a thousand children, sample sizes for the included studies were variable. For some countries, few studies were available, or studies that were available had information on a relatively small number of AML cases, which may have artificially raised the calculated ratio of APL to AML cases — the country with the highest ratio of APL to AML (58.8% in Nicaragua) had a smaller study size (n=17). However, a number of studies where the proportion of APL was greater than 20% or less than 5% had relatively larger study sizes, or multiple studies, suggesting that the variation in the geographic distribution of APL observed was not due to study size alone.

Gender difference in childhood APL varies with study size

Gender ratios of *de novo* APL studies gathered in this review are presented in Figure 3 and Supplementary Tables S1a–b. We did not find evidence (Figure 3) supporting a predominance of either gender in the APL studies. When study sizes were small, in the *de novo* cases of APL examined, predominance of male or females was often present, but across the two different groups examined, AML studies with APL data and APL only studies (a and b in Table 1, respectively), as study size increased, gender differences became less apparent (Figure 3, Supplementary Tables S1a–b). For example, in data taken from Yeh *et al*, the gender ratio (male/female) was 5/1, showing a clear male predominance [135]. Contrastingly, data from Gilbert *et al* showed a clear female predominance with a gender ratio of 3/6 [182]. In both cases, study sizes were small (n=6 and n=9, respectively). The gender ratio was approximately 50:50 in larger studies, as reflected by studies by Guglielmi *et al* (n=63, gender ratio: 33/30) and Biondi *et al* (n=54, gender ratio: 28/26) [83, 191].

Childhood t-APL exemplifies the association between APL and exposure to chemicals

In the current review, 38 pediatric t-APL cases were identified from 30 studies (several studies presented multiple cases of t-APL) in the literature (Table 1, Supplementary Table S2) [36, 37, 206–233]. Ten of these cases were excluded from analysis (Table 3) due to lack of cytogenetic information (the cases were diagnosed by morphology alone) or cytogenetics inconsistent with APL. Characteristics of the final 28 cases are presented in Table 3, and include age at diagnosis of t-APL, gender, latency (time to APL), cytogenetics, primary disease, treatment, and outcome. More detailed information is provided in Supplementary Table S2.

Characteristics and primary diseases of childhood t-APL cases—The age at t-APL diagnosis ranged from 2–21 years, with a median age of 10 years and a mean age of 11.4 years (Table 3, Figure 4a). In contrast to the *de novo* APL findings, in the 28 cases of childhood t-APL included in this review, there was a female predominance of 57% (16 girls versus 12 boys) though the case studies collected provide a limited view which may not be representative of the entire population. Primary diseases included Langerhans cell histiocytosis (LCH), multiple sclerosis (MS), Hodgkin lymphoma (HL), psoriasis, non-Hodgkin lymphoma (NHL), and assorted solid tumors. Among the cases included, the most common primary diseases were LCH, HL, and a variety of solid tumors, which accounted for 25%, 14% and 21% of the included primary diseases, respectively. Excluding leukemia, other hematological disorders—LCH, HL and NHL—comprised 61% of the total primary diseases prior to therapy-related APL.

Treatment for primary disease—Depending on primary malignancy, treatment for primary disease was variable. Even within cases with the same primary malignancy, there were differences in treatments for individual cases. It has previously been established that exposure to radiation and chemotherapy drugs including mitotic inhibitors and alkylating agents involved in the treatment for a variety of primary malignancies or conditions are associated with the development of t-APL and AML in children [34, 36]. Consistent with this result, in the cases included in this review, the most frequently used drugs to treat primary malignancies prior to secondary APL were topoisomerase II inhibitors (i.e. etoposide, mitoxantrone) and anthracyclines, alkylating agents (i.e. cyclophosphamide, dicarbazine) and vinca alkaloids (i.e. vinblastine, vincristine). In many cases combinations of drugs and radiotherapy were employed. In two cases, secondary APL developed following radiation alone.

Latency definition and distribution—In the cases included, definitions of latency (time to APL) were varied. In this review, latency was defined as either the time from diagnosis of primary disease to development of t-APL or the time from beginning of treatment for primary disease to development of t-APL, depending on the information available from the original studies. For the purposes of this study, we assumed that the time between diagnosis of primary disease and beginning of treatment was negligible allowing us to compare latencies across cases.

A median of 32 months (Table 3, Figure 4b) and a mean of 35.8 months were calculated from 24 cases listed in Supplementary Table S2 (latency information was not available for one case, and three cases were excluded from calculations in Table 3 and Figure 4b due to definitions of latency inconsistent with our definition). Latency times that we recorded were highly varied — development of APL occurred as quickly as 18 months following interruption of primary therapy in one case study or after more than 6 years (72 months) in another (Figure 4b). Information on APL latency (time to APL) indicates that in the majority of cases, t-APL developed within roughly 1–3 years after treatment for the primary illness.

Cytogenetics and prognosis—For cases where cytogenetic information was available (n=26), the majority (84%) of cases had characteristic t(15;17) cytogenetics. Two cases (8%) showed more rare t(5;17) cytogenetics and one case featured a t(11;17) translocation. Of the 28 cases, there were 19 cases with available information regarding prognosis: complete remission following treatment for APL (n=16) and death (n=3). Because the APL case studies included span several decades, it is important to take into account improved outcomes as therapy and supportive care has changed.

While a previous study by Ogami *et al*, provided a review of 15 cases of pediatric t-APL [228], the current study provides an updated and expanded view of t-APL, examining 28 cases of t-APL in children and adolescents up to 21 years old. While the case studies described here provide some insight into childhood t-APL, there is a lack of comprehensive data regarding the proportion of children that develop APL after treatment for a primary disease.

Comparison of t-APL in children and adults

Twenty-six studies that included information on t-APL in adults, representing a total of 260 cases (age > 21), were identified from the literature (Supplementary Table S3) and are summarized in Table 4 [38, 40, 208, 214, 216, 220, 234–253]. Of the 24 studies that included information about gender, 98 were men and 150 were women. In adult t-APL cases, there was a similar female predominance to childhood t-APL (60% vs 59%, respectively). Among these adults, the most common primary diseases prior to development of APL were breast cancer (94 cases), multiple sclerosis (51 cases) and prostate cancer (21 cases). Similarly, an earlier review examined 326 adult cases of t-APL from the literature and reported the most common conditions prior to therapy-related APL were breast cancer, hematological malignancies, multiple sclerosis and genitourinary malignancies [264]. Hematological malignancies and multiple sclerosis were also among the most frequent diseases prior to childhood t-APL, as discussed in the previous section (Table 3).

Similar to children, some of the most common treatments prior to development of t-APL in adults were treatment with topoisomerase II inhibitors/anthracyclines, alkylating agents, and radiation therapy. Radiation was involved in therapy for 153 of the cases (Table 4). Time to APL diagnosis varied among studies, ranging from as short a period of time one month to as long as 276 months.

Environmental and occupational exposure related factors associated with APL

One of the goals of our study was to examine the potential contribution of exposure-related risk factors to geographic variations in childhood APL. However, few studies have specifically examined childhood APL and exposure.

Increased risk of APL—In one of two cases examined in a single study, a t(15;17) translocation was determined to have arisen prenatally, over 10 years before clinical manifestation of childhood APL [265]. Though confirmation in additional patients is needed, it is probable that prenatal and postnatal exposures may play a role in the origination and development of childhood APL. *In utero* exposure to ionizing radiation [43], 3rd trimester air toxics exposures to chloroform, benzene, and two other traffic-related chemicals (meta/para-xylene and toluene) [45], and parental smoking [44], as well as childhood exposure to petroleum solvents [42] are potentially assosicated with development of childhood AML. Increased risk of childhood ALL has been associated with accelerated fetal growth [266], home exposure to herbicides (chlorthal, and possibly alachlor) [267] and paint [42], paternal ever smoking, particularly preconception [268]. Elevated ALL risks associated with use of paints in the home (ever) and indoor insecticides (pre-birth) were found to be limited to subjects carrying specific haplotypes of *CYP2C8* and *ABCB1*, respectively [269]. Exposure to benzene, a well-known risk factor for adult AML, may also be associated with both childhood ALL and AML [270]. Larger studies are needed to determine the risk of these prenatal and postnatal exposures on development of childhood APL and the contribution of genetic susceptibility.

In adults, an increased risk of APL has been previously associated with various environmental, occupational and life-style related risk factors. For this review, ten studies (6

case-control studies and 4 case series studies) suggesting an association between certain risk factors and APL in adults were identified and are summarized in Table 5 [254–263]. Occupational and industrial exposures associated with an increased risk of APL included general construction (OR=2.28, 95% CI=1.03–50.05), metal work (OR=14.00, 95% CI=1.72–113.77) [254] and shoe making (OR= 6.3, 95% CI=1.2–31.1) [255]. The study authors suggest that the relationship between APL and shoe making is potentially related to exposure to benzene, which is present in glues used for shoe making [255].

Benzene exposure and APL—Additional previous studies have supported an association between benzene exposure and development of APL. In a case-control study by Richardson *et al* examining occupational risk factors for acute leukemia, the authors reported that exposed cases, (which included workers exposed to benzene), had more AML-M3 subtypes than non-exposed cases (7.8% versus 5.2%) [271]. One case of APL was also reported in benzene-exposed workers in a study by Yin *et al* in China [263]. In addition, in a cohort study of benzene-exposed Chinese factory workers, APL was the most common form of AML diagnosed, representing 4 out of a total of 9 AML cases [260]. In a study by Wong *et al* (2010) of 722 newly diagnosed AML cases and 1,444 individually gender- and aged-matched patient controls in Shanghai, a borderline significant risk (OR= 1.95, 95% CI=0.98–3.88) of almost two-fold was found between benzene exposure and APL development (Table 5). This study, as well as an additional study by the same author (Wong *et al*, 2009) found that home and workplace renovation was associated with an increased risk for APL (OR= 2.01, 95% CI=1.01–4.00) and OR=2.02, 95% CI=1.06–3.85, respectively) in adults in Shanghai [254, 259]. These studies named paints, adhesives, glues, solvents, preservatives, dusts, treated fabrics and building materials as potential exposures present in these environments, specifically noting the high benzene levels associated with Chinese commercial painting and elevated levels of formaldehyde and benzene (known human leukemogens) as well as toluene, xylene and other volatile organic chemicals in newly renovated homes in China [254, 259].

Body mass index, smoking and APL—With regards to life style and environment, increased body mass index (BMI) was reportedly associated with APL, with ORs increasing with increasing BMI (p_{trend} = 0.03, Table 5), in adults in Shanghai [259]. In a study by Estey *et al*, increasing BMI in adults was associated with diagnosis of APL [262]. Similarly, in children, obesity at diagnosis has previously reported to be associated with APL. In a study of fifty children by Feusner *et al*, 13 of them (26%) were obese, compared to an expected overall incidence of 11% in a healthy pediatric population [31]. In the studies we identified that examined associations between smoking and specific AML subtypes, an association between smoking and development of APL was not found [256, 257].

CONCLUSIONS

This study provides the first comprehensive overview of global variation in the proportion of childhood APL among AML cases. In the 142 studies gathered, we found the lowest percent of APL among AML in Switzerland (2.4%) and the highest in Nicaragua (58.8%). Compared to North America, the assessed APL risk among AML cases was more than two times higher in South/Central America (OR=2.43, 95% CI=1.70–3.47). A goal of this study

was to examine whether known or potential environmental exposures and lifestyle-related factors may contribute to this apparent global variation. Due to the limited number of studies directly addressing childhood APL development and exposure, we examined 28 childhood cases of therapy-related APL, which exemplified associations between prior exposures to chemotherapeutic drugs and APL development.

FUTURE DIRECTIONS

More studies examining both the incidence of APL, in countries and regions for which information is lacking, and the association of APL with specific risk factors are needed. In this review, we have examined the distribution of APL mostly in hospital- and study-based populations; further studies examining the distribution of APL using population-based data like national and/or regional cancer registries are needed. Since APL is a relatively rare subtype of acute childhood leukemia, studying exposure from individual studies is difficult. The Childhood Leukemia International Consortium (CLIC) may be better positioned to study APL [272].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS LIST

ALL	Acute Lymphocytic Leukemia
AML	Acute Myeloid Leukemia
APL	Acute Promyelocytic Leukemia
ATRA	All-trans Retinoic Acid
BMI	Body Mass Index
CI	Confidence Interval
CLIC	The Childhood Leukemia International Consortium
FAB	French-American-British
HL	Hodgkin Lymphoma
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems

LCH	Langerhans Cell Histiocytosis
MS	Multiple Sclerosis
NHL	Non-Hodgkin Lymphoma
OR	Odds Ratio
t-AML	Therapy-related AML
t-APL	Therapy-related APL
WHO	World Health Organization

PRACTICE POINTS

- Geographic patterns may potentially reflect specific genetic and environmental factors involved in development of APL.
- In light of increasing globalization, where patients have lived previously may have increasing relevance to their risk of APL.
- A predominance of either gender in *de novo* childhood APL was unclear. Although in the t-APL cases gathered a female predominance was observed, the number of cases was too few to draw conclusions about a potential gender difference.
- Development of t-APL in children is potentially associated with exposure to certain chemotherapy drugs/radiation given for treatment for a primary disease.

RESEARCH AGENDA

- Geographic distribution of childhood APL using population-based data from registries
- Contribution of specific environmental factors to childhood APL risk
- Association between obesity and APL in children

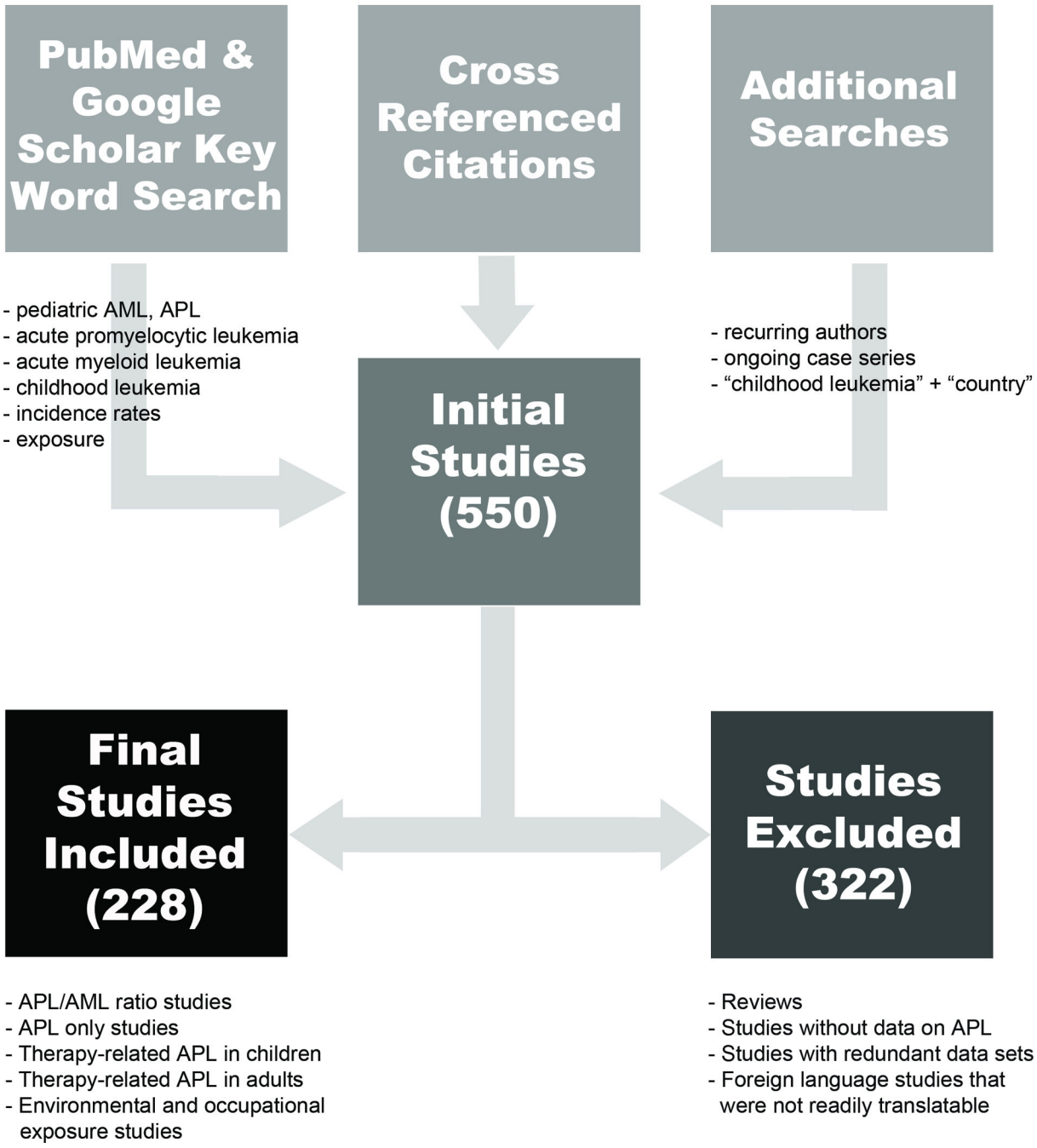

Figure 1. Study selection process

This flow diagram depicts the logic of the study selection process, the results of which are included in this review. In total, 228 studies were included.

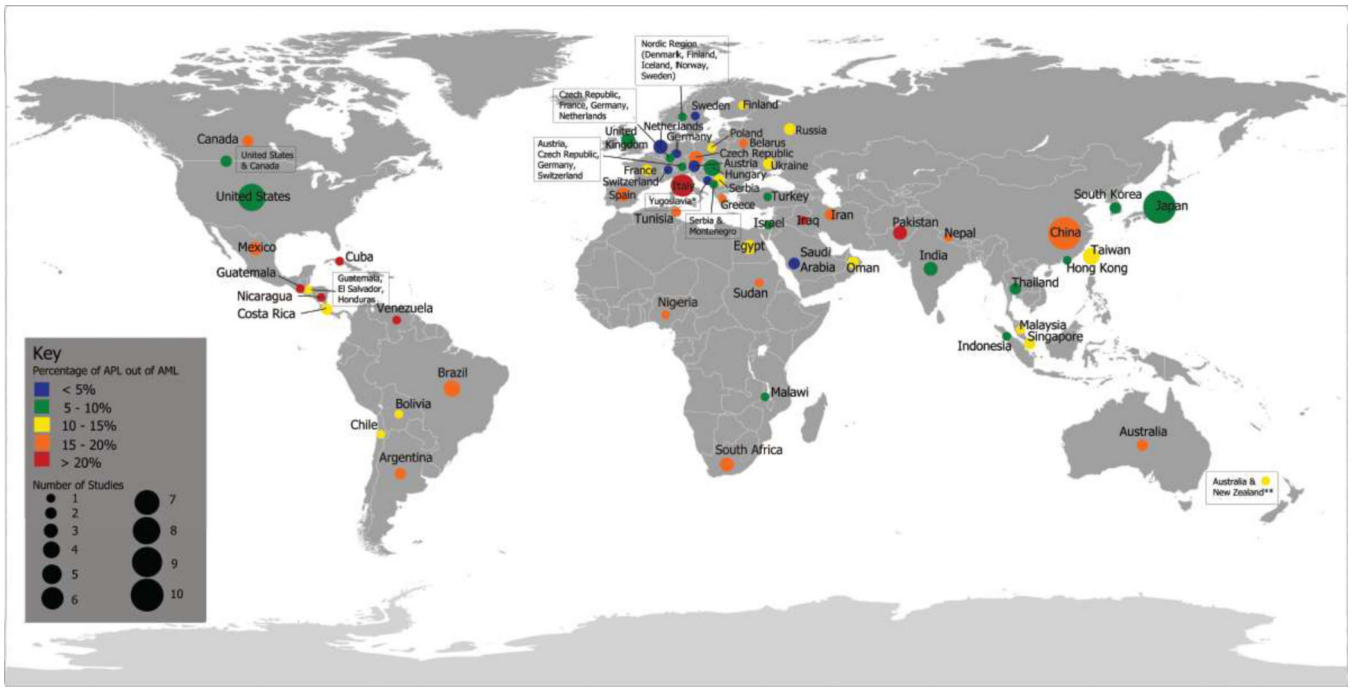

Figure 2. Global map of *de novo* childhood APL as a percentage of AML

The percentage of childhood AML cases comprised of APL cases was calculated for each country by averaging all the studies collected for that country. *Study was conducted in region formerly known as Yugoslavia, which includes present day nations of Serbia, Montenegro, Slovenia, Croatia, Bosnia and Herzegovina and the Republic of Macedonia. **One study contained data from patients in both Australia and New Zealand.

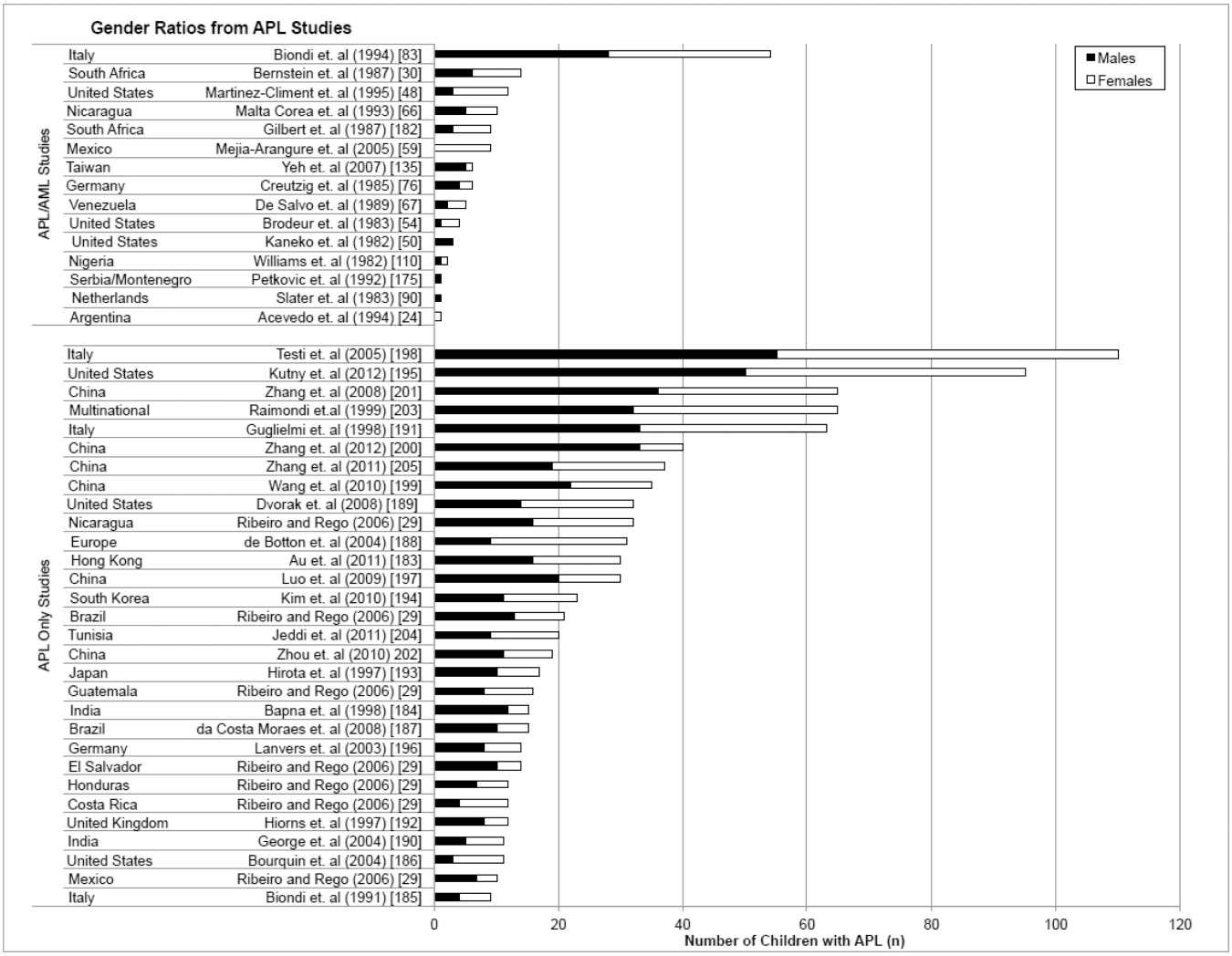

Figure 3. Gender ratios for APL in children

To examine gender, the *de novo* childhood APL studies were divided into two groups: APL/AML Studies and APL Only Studies. “APL/AML” contained data from studies previously reported in Table 2. “APL Only Studies” contained no information regarding the proportion of APL among AML cases and are represented here for the first time.

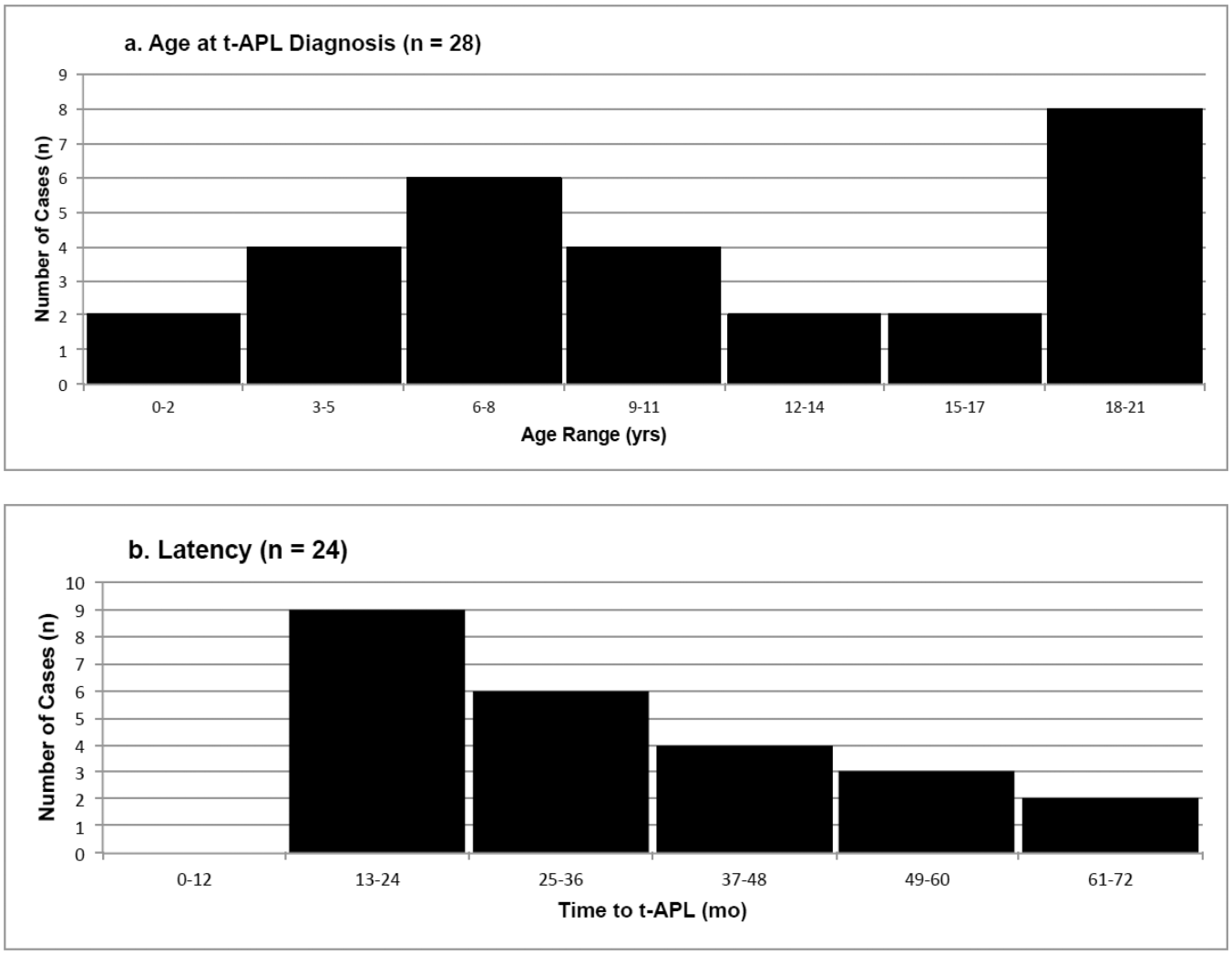

Figure 4. a–b Distribution of data from therapy-related APL studies in Children

Figure 4a depicts age (in years) at t-APL diagnosis for n=28 cases. Figure 4b depicts time to APL (latency) for n=24 cases.

Table 1

Organization of Studies Included in this Review (N = 228)

Study Category	Study (N)	Presented In	
Regional Studies: Ratio of APL/AML	**142**		
North America	13	Table 2a	Figure 2
South & Central America	14	Table 2b	
Europe	38	Table 2c	
Africa & Middle East	19	Table 2d	
Asia	40	Table 2e	
Oceania & Multinational	18	Table 2f	
APL Studies with Gender Information			
a. APL/AML studies	15[a]	Supplementary Table S1a	Figure 3
b. APL only studies	**24**	Supplementary Table S1b	
Therapy-related APL Studies	**52**[b]		
Children	30	Table 3, Supplementary Table S2	Figure 4a–b
Adults	26	Table 4, Supplementary Table S3	
Environmental & Occupational Exposure Studies	**10**	Table 5	

[a] 15 studies which contained information about the ratio of APL/AML (Table 2a–f) also contained information about gender.

[b] Four studies contained case studies with information about children and adults: Beaumont et. al (2003), Ellis and Bogglid (2009), Ottone (2012), Hasan et. al (2010) [208, 220, 216, 214].

Table 2

a. Distribution of De Novo Childhood APL Cases as a Percentage of AML in North America

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
North America												
United States (6.2%)	N/A	Clinical Trial	Cohort of survivors analyzed.	Orgel et. al (2013) [47]	COG	2004 – 2009	0.3 – 18.6	52	0	0.0	N/A	x
	N/A	Case Series	Absence of prior history of malignant disease or cytotoxic therapy; deceased cases included.	Martinez-Climent et. al (1995) [48]		Jul 1981 – Dec 1993	< 20	115	12	10.4	x	x
	California, Michigan, Minnesota, New York, Texas, Utah, Washington DC	Case Series	Children diagnosed with ALL or AML who were refractory to primary therapy or experienced relapse and received treatment at participating TACL institutions; deceased cases included.	Gorman et. al (2010) [49]	TACLT2005-002	1995 – 2004	0 – 21	99	8	8.1	N/A	x
	Chicago	Case Series	Patients admitted consequtively to the University of Chicago Hospitals and	Kaneko et. al (1982) [50]		Jun 1977 – Jun 1981	≤ 16	26	3	11.5	x	x

a. Distribution of De Novo Childhood APL Cases as a Percentage of AML in North America

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
			Clinics (11), Children's Memorial Hospital (11), University of Illinois (1), Columbus Hospital (1) and Saitama Center (2).									
	Tennessee	Clinical Trial	Patients with secondary leukemia, MDS, excluded. Patients with DS excluded for AML 83, 87 and 97 protocols.	Ribeiro et. al (2005) [51]	SJCRHAML 80	1980 – 1983	< 15	65	1	1.5	x	x
					SJCRHAML 83	1983 – 1987	< 15	45	4	8.9	x	x
					SJCRHAML 87	1987 – 1991	< 15	39	4	10.3	x	x
					SJCRHAML 91	1991 – 1996	< 15	62	1	1.6	x	x
	Tennessee	Case-Control	Treatment for AML at St. Jude Children's Research Hospital.	Okamoto et. al (2003) [52]	SJCRH	1991 – 2000	N/A	172	2	1.2	x	x
	Tennessee	Case Series	Treatment for AML at St. Jude Children's Research Hospital; children with DS and s-AML excluded.	Raimondi et. al (1989) [53]	SJCRH	Apr 1980 – Mar 1987	N/A	121	9	7.4	x	x
	Tennessee	Case Series	Consequtively admitted to St. Jude Children's Research Hospital.	Brodeur et. al (1983) [54]	SJCRH	Jul 1978 – Dec 1981	≤ 19	73	5	6.8	x	x

a. Distribution of De Novo Childhood APL Cases as a Percentage of AML in North America

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
Canada (16.0%)	Saskatchewan	Case Series	Children with AL in Regin, Saskatoon clinics of Saskatchewan Cancer Commission; deceased patients included unless lost for follow-up.	McSheffrey et. al (1975) [55]		1966 – 1972	0 – 16	15	2	13.3	N/A	x
	Toronto	Case Series	Children with s-AML excluded.	Abdelhaleem (2007) [56]		2000 – 2006	< 18	59	11	18.6	x	x
Mexico (16.4%)	N/A	Case Series	N/A	Dorantes-Acosta et. al (2008) [57]		N/A	1 – 14	17	3	17.6	x	x
	Mexico City	Case Series	Residents of Mexico City, newly diagnosed leukemia treated in a hospital in Distrito Federal.	Perez - Saldivar et. al (2011) [58]		2006 – 2007	< 15	28	3	10.7	N/A	x
	Mexico City	Case Series	Children at Pediatric Hospital and General Hospital of Mexican Social Security Institute in Mexico City. Only children who are Mexican nationals or whose parents	Mejia-Arangure et. al (2005) [59]		1996 – 2000	0 – 14	43	9	20.9	N/A	x

a. Distribution of De Novo Childhood APL Cases as a Percentage of AML in North America

Region	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML	APL	APL/AML	Methods for APL Classification	
(average %: APL/AML)								(n)	(n)	(%)	Cytogenetics t(15;17)	Morphology (FAB)
			were residents of Mexico City included.									

b. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in South & Central America

Region	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML	APL	APL/AML	Methods for APL Classification	
(average %: APL/AML)								(n)	(n)	(%)	Cytogenetics t(15;17)	Morphology (FAB)
South & Central America												
Argentina (18.8%)	N/A	Case Series	Children with DS, s-AML excluded.	Acevedo et. al (1994) [24]		1990 – 1992	0 – 15	17	1	5.9	x	x
	La Plata	Case Series	Previously untreated patients at Sor Maria Ludovica Hospital.	Gomez et. al (2001) [60]		Apr 1994 – May 1999	≤ 16	41	13	31.7	x	x
Bolivia (10.5%)		Case Series	Leukemias diagnosed in la Unidada de Biologica Celular de las Facultad de Medicina de la UMSA of Bolivia; patients with biphenotypic leukemia excluded.	Amaru et. al (2012) [180]		Jan 1999 – May 2012	0 – 18	172	18	10.5	x	x
Brazil (15.1%)	N/A	Case Series	Age range for criteria was 0–23 months, but 39 children aged 18–23 months included to account for delay in	Emerenciano et. al (2006) [61]	BCSGIL	Jan 1998 – Jan 2005	< 2	62	5	8.1	x	x

b. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in South & Central America

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
			identification of acute leukemia in areas of Brazil; patients with MDS, DS excluded.									
	Hospital das Clínicas, Universidade Federal de Minas Gerais	Clinical Trial	Children with previous history of chemotherapy, treatment with protocol designed for adults, MDS or death before treatment start excluded.	Viana et. al (2003) [181]		1986 – 2000	< 16	83	18	21.7	N/A	x
	Rio Grande do Sul	Case Series	Patients treated at Hospital de Clinicas de Porto Alegre, which treats patients from Brazilian state Rio Grande do Sul; patients with s- AML, MDS, history of chemotherapy or CML excluded.	Onsten et. al (2006) [62]		1990 – 2002	< 20	47	13	27.7	x	x
	South, Southeast, Northeast, Middle West regions of Brazil	Case Series	Childhood leukemia associated with DS, monosomy 8, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, neurofibromatosis, MDS, and children older than 24 months excluded.	Emerenciano et. al (2013) [63]	BCSGIAL	Jan 2000 – Jan 2011	≤ 2	160	5	3.1	x	x
Costa Rica (10.2%)	N/A	Registry[a]	Newly diagnosed leukemia; deceased cases included.	Monge et. al (2002) [2]		1981 – 1996	< 15	144	19	13.2	N/A	x

b. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in South & Central America

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
	San Jose	Case Series	Patients referred to National Children's Hospital (only reference center for pediatric hematology in country); cases of s-AML, MDS excluded.	Santamaria-Quesada et. al (2009) [64]		Jan 2006 – May 2007	< 14	14	1	7.1	x	x
Cuba (31.3%)	All Cuban Provinces	Case Series	N/A	Hernandez et. al (2000) [7]		Jan 1993 – Dec 1997	< 15	83	26	31.3	x	x
Chile (13.9%)	N/A	Clinical Trial	Newly diagnosed AML at 11 Chilean hospitals; patients with DS, secondary myeloblastic leukemia and myelosarcoma excluded.	Quintana et. al (2005) [5]	PINDA 87	Mar 1987 – Nov 1991	< 15	106	12	11.3	x	x
					PINDA 92	Jan 1992 – Jan 1998	< 15	151	25	16.6	x	x
Guatemala (34.4%)			Results obtained at Unidad Nacional de Oncologia Pedatrica in Guatemala City, Guatemala, referral center for whole country. Patients with previous chemotherapy or assesment of nutritional status more than 48 hours after beginning chemotherapy excluded. MDS excluded from	Sala et. al (2008) [65]		Oct 2004 – Sept 2006	1 – 18	32	11	34.4	N/A	N/A

b. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in South & Central America

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
			analysis.									
Nicaragua (58.8%)	N/A	Case Series	Patients referred to Managua Children's Hospital, only pediatric hematology-oncology service in country.	Malta Corea et. al (1993) [66]		1990 – 1992	6 – 15.5	17	10	58.8	x	x
Venezuela (26.3%)	Zulia	Case Series	Patients referred to Instituto Hematologico de Occidente.	De Salvo et. al (1989) [67]		1982 – 1987	< 10	19	5	26.3	x	x

c. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Europe

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
Europe												
Austria (4.4%)	Vienna	Case Series	Children with AML or TMD diagnosed in Austria, registered at single institution.	Strehl et. al (2001) [68]		1993 – 1998	0.01 – 16.4	67	5	7.5	x	x
	Vienna	Case Series	N/A	Haas et. al (1993) [69]		1978 – 1989	N/A	71	1	1.4	x	x
Belarus (18.5%)	N/A	Registry *a*	Treatment at Belarusian Center for Pediatric Oncology, which treats more than	Lipay et. al (2011) [70]		2000 – 2009	0.8 – 21	151	28	18.5	N/A	N/A

c. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Europe

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
			70% of children in Belarus with cancer.									
Czech Republic (18.5%)	N/A	Clinical Trial	Patients with death before treatment, s-AML, major protocol violations, MDS and DS excluded.	Sramkova et. al (2013) [71]	AMLBFM 1993 /1998	Jun 1993 – Feb 2004	0 – 19	125	11	8.8	x	x
					AMLBFM 2004	Mar 2004 – Dec 2009	0 – 18	57	9	15.8	x	x
	N/A	Case Series	All children diagnosed and treated in Czech Pediatric Hematology Working Group centers.	Burjanivova et. al (2006) [72]		N/A	1 – 14	13	4	30.8	x	N/A
Finland (10.5%)	N/A	Case Series	Patients diagnosed and treated at Hospital for Children and Adolescents, Helsinki University Central Hospital and Kuopio University Hospital, Finland.	Huhta et. al (1999) [73]		N/A	1–15.6	19	2[b]	10.5	x	x
France (11.3%)	Paris	Case Series	Treated at Hopital Saint Louis; previously treated patients excluded.	Leverger et. al (1988) [74]		Sept 1977 – Dec 1986	< 16	130	11	8.5	x	x
	Paris, Lille	Case Series	Diagnosed at Trousseau Hospital, Claude Huriez Hospital.	Lapillonne et. al (2006) [75]	LAME 88/91 LAME 99 (APL)	Mar 1993 – Jan 2002	0.003 – 18.7	92	13	14.1	x	x

c. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Europe

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
Germany (4.0%)	West Germany	Clinical Trial	Children treated in 30 West German hospitals without prior malignancy or without prior treatment for more than 14 days; three infants with congenital leukemia, DS excluded.	Creutzig et. al (1985) [76]	AMLBFM 78	Dec 1978 – Oct 1982	< 17	151	6	4.0	N/A	x
Greece (15.8%)	N/A	Case Series	N/A	Manola et. al (2013) [77]		1998 – 2010	≤ 21	133[c]	21	15.8	x	x
Hungary (6.5%)	N/A	Clinical Trial	N/A	Szegedi et. al (2013) [78]	HPOG AMLBFM 98	2001 – 2011	< 18	112	9	8.0	x	x
	N/A	Case Series	Children diagnosed at 10 centers of Leukemia Working Party in Hungary.	Revesz et. al (1985) [79]		1971 – 1982	< 15	123	2	1.6	N/A	x
	N/A	Case Series	Patients in Hungarian Study Group on Childhood Leukemia.	Keleti et. al (1978) [80]		1971 – 1975	N/A	41	2	4.9	N/A	x
	Budapest	Case Series	Newly diagnosed AML at Semmelweis University or another pediatric hematological center in Budapest.	Haltrich et. al (2006) [81]		1997 – 2003	0.58 – 18	26[d]	3	11.5	x	x
Italy (21.9%)	N/A	Clinical Trial	Newly diagnosed AML, patients	Pession et. al (2005) [82]	AEIOP LAM-87	Jan 1987 – Feb 1993	0 – 15	151	27	17.9	x	x

c. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Europe

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
			with granulytic sarcoma, MDS, DS, s- AML or pretreatment > 14 days excluded.		AEIOP LAM-87M	Feb 1989 – May 1993	0 – 15	77	20	26.0	x	x
	N/A	Registry [a]	Newly diagnosed AML admitted and treated at 29 AEIOP institutions.	Biondi et. al (1994) [83]	AEIOP	Apr 1989 – Nov 1993	< 15	314	54	17.2	x	x
	Catania, Florence, Genoa, Monza, Padua, Rome, Trieste, Turin	Case Series	Admitted to treatment at one of 8 Italian centers.[e]	Castagnola et. al (2010) [84]		Jan 1998 – Dec 2005	< 15	240	33	13.8	N/A	x
	Monza	Case Series	Diagnosed at Clinica Pediatrica Universita di Milano Bicocca.	Arrigoni et. al (2003) [85]		Jan 1985 – Dec 2000	< 18	119	32	26.9	x	x
	Monza	Case Series	Pediatric AML cases observed at Clinica Pediatrica Universita di Milano.	Cantu-Rajnoldi et. al (1993) [86]		1970 – 1992	N/A	151	46	30.5	x	x
	Piedmont	Registry [a]	N/A	Maule et. al (2008) [87]		1980 – 2003	< 15	121	26	21.5	x	x
Netherlands (4.5%)	N/A	Clinical Trial	Newly diagnosed AML; patients with corticosteroids or chemotherapy longer > 2 weeks before diagnosis, DS, myelosarcoma, MDS excluded.	Kardos et. al (2005) [88]	DCOG AML-82	Jan 1983 – Jun 1987	0 – 15	48	2	4.2	N/A	x
					DCOG AML-87	Jun 1987 – Oct 1992	0 – 15	83	3	3.6	x	x
					DCOG AML: 92/94	Oct 1992 – Jun 1998	0 – 15	78	2	2.6	x	x

c. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Europe

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
	N/A	Clinical Trial	Newly diagnosed AML.	De Bont et. al (2002) [89]	DCLSG	1988 – 1998	0–14	47	3	6.4	x	x
	Amsterdam	Case Series	AML referred to Emma Children's Hospital and the Academic Hospital of the Free University in Amsterdam.	Slater et. al (1983) [90]		N/A	0.08 – 15.25	17	1	5.9	x	x
Poland (10.5%)	N/A	Clinical Trial	AML with absence of severe congeinital malformations or comorbitities included. Patients with AML following CML, MDS, s-AML, congenital malformations and severe comorbidities including DS, biphenotypic leukemia, death before treatment and pre-treatment with other protocols or incomplete data excluded.	Balwierz et. al (2013) [91]	PPLLSG 83	1983 – 1994	0.1 – 16.6	208	23	11.1	N/A	x
					PPLLSG 94	1994 – 1997	0.6 – 16.6	83	9	10.8	x	x
					PPLLSG 98	1998 – 2004	0.1 – 17.8	195	23	11.8	x	x
					PPLLSGAMLBFM 2004	2005 – 2011	0.006 – 18.1	237	20	8.4	x	x
Russia (14.4%)	N/A	Case Series	Patients at Russian Children's Clinical Hospital.	Nasedkina et. al (2003) [92]		N/A	N/A	76	10	13.2	x	N/A
	Moscow	Case Series	Admitted to the Federal Research Center for Pediatric Hematology, Oncology and	Yatsenko et. al (2013) [93]		2006 – 2010	< 17	186	29	15.6	x	x

c. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Europe

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
			Immunology.									
Serbia (11.2%)	N/A	Case Series	N/A	Krstic et. al (2010) [94]		N/A	1 – 15.6	19	3	15.8	x	N/A
	Belgrade	Case Series	Diagnosed at University Children's Hospital and Mother and Child Healthcare Institute.	Krstovski et. al (2010) [95]		Jan 1997 – June 2007	N/A	92	6	6.5	x	x
Spain (15.3%)	Barcelona	Case Series	Patients diagnosed and treated at Hospital Vall d'Hebron and Hospital Sant Joan de Deu in Barcelona.	Armengol et. al (2010) [96]		1992 – 2002	< 17	63[f]	8	12.7	x	x
	Catalonia	Clinical Trial	Previously untreated AML included in AML-88 Trial.	Ortega et. al (2003) [97]		Apr 1988 – May 2001	< 15	79	10	12.7	x	x
	Girona, Valencia, Zaragoza	Registry [a]	Deceased cases included.	Marco s-Gragera et. al (2010) [98]		1993 – 2002	< 15	63	13	20.6	N/A	x
Sweden (2.9%)	Southern	Case Series	N/A	Andersson et. al (2008) [99]		1995 – 2004	0 – 17	34	1	2.9	x	N/A
Switzerland (2.4%)	N/A	Case Series	DS AML included.	Betts et. al (2007) [100]	SPOG	Sept 1994 – Jan 2005	0 – 16	82[g]	2	2.4	x	x

c. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Europe

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
Ukraine 11.3%)	N/A	Case Series	Registered at the Institute of Haematology and Transfusiology AMS Ukraine.	Andreieva et. al (2010) [101]		1992 – 2008	0.33 – 18	116	13	11.2	x	x
	Kiev	Case Series	Data from Reference Lab for leukemia diagnostics established by Haematopathologists for Patients with Malignant Diseases of the Blood. Survey covers all cases of childhood leukemia registered during the indiciated period for these regions according to the Ukraine Ministry of Health.	Gluzman et. al (1999) [102]		1993 – 1997	0 – 17	44	5	11.4	N/A	x
United Kingdom (7.6%)	N/A	Clinical Trial	Patients with s-AML, DS, MDS, bilineage leukemia excluded from analysis.	Gibson et. al (2005) [103]	MRCAML 10	May 1988 – Mar 1995	0 – 14	303	27	8.9	x	x
					MRCAML 12	Apr 1995 – May 2002	0 – 14	455	40	8.8	x	x
	N/A	Case Series	Patients referred to the Hospital for Sick Children; all children referred for treatment included, even those that died within hours of admission.	Phillips et. al (1991) [104]		1972 – 1987	N/A	152	10	6.6	N/A	x
	England, Scotland, Wales	Registry [a]	N/A	c		1980 – 1988	< 15	471	28	5.9	N/A	x

d. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Africa and the Middle East

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL /AML (%)	Methods for APL Classification	
											Cytogeneticst (15;17)	Morphology (FAB)
Africa												
Egypt (13.2%)	N/A	Case Series	Newly diagnosed AML admited to Mansoura University Children's Hospital.	Al-Tonbary et. al (2009) [106]		Jan 2004 – Jan 2007	1 – 15	30	6	20.0	x	x
	N/A	Registry[a]	Treated at Children's Cancer Hospital Egypt, which receives patients from all Egyptian governorates.	Ezzat (Personal Correspondence, 2012) [107]		Jul 2007 – Dec 2011	0 – 18	353	34	9.6	N/A	N/A
	Cairo	Case Series	AL at Pediatrics Hospital, Ain Shams University.	Ismail et. al (2012) [108]		Nov 2007 – Apr 2011	1 – 15	30	3	10.0	x	x
Malawi (6.3%)	Blantyre	Case Series	Diagnosed at Queen Elizabeth Central Hospital.	Mukiibi et. all (2001) [109]		Jan 1994 – Dec 1998	0 – 15	16	1	6.3	N/A	x
Nigeria (18.2%)	Ibadan	Case Series	Indigenous Nigerian residents of Ibadan and surrounding rainforest.	Williams et. al (1982) [110]		Jul 1978 – Dec 1981	≤ 14	11	2	18.2	N/A	x
South Africa (17.9%)	Cape Province/ Eastern Cape	Case Series	Diagnosed at Red Cross War Memorial Children's Hospital, major referral center for Cape	Gilbert et. al (1987) [182]		Jan 1981 – Dec 1985	0.67 – 10.92	43	9	20.9	x	x

d. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Africa and the Middle East

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL /AML (%)	Methods for APL Classification	
											Cytogeneticst (15;17)	Morphology (FAB)
			Province, with select patients from neighboring provinces and countries.									
	Johannesburg	Case Series	Diagnosed at three main teaching hospitals attached to University of the Witwatersrand Medical School.	Bernstein et al (1984) [30]		Jan 1978 – Apr 1982	0 – 15	26	5	19.2	x	x
	Johannesburg	Case Series	Newly diagnosed, untreated AL referred to Childrens Hematology /Oncology Clinics at Transvaal Memorial Hospital for Children, Joahnnesbug Hospital and Baragwanth Hospital.	Macdougall et. al (1986) [111]		Jan 1974 – Dec 1982	0 – 15	52	7	13.5	x	x
Sudan (18.2%)	N/A	Case Series	Cases diagnosed at University of Khartoum Department of Pathology/National Health lab which serves hospitals in three towns of Khartoum province.	Ahmed et. al (1982) [112]		Jan 1970 – Dec 1976	2 – 19	11	2	18.2	N/A	x

d. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Africa and the Middle East

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL /AML (%)	Methods for APL Classification: Cytogeneticst (15;17)	Methods for APL Classification: Morphology (FAB)
Tunisia (16.5%)		Case Series	Consecutive ethnic Tunisian patients.	Gmidene et. al (2012) [113]		Jan 2000 – Dec 2007	0 – 16	97	16	16.5	x	x
Middle East												
Iraq	Baghdad	Case Series	Diagnosed at Pediatric Oncology Unit at Al-Mansour Pediatric Hospital, referral center for childhood cancer in Iraq.	Testi et. al (2006) [114]		Jan 2002 – Jan 2003	< 15	32	11	34.4	N/A	x
(34.5%)						Oct 2003 – Aug 2004	1 –15	26	9	34.6	N/A	x
Iran (16.0%)	Tehran	Case Series	Consecutive patients referred to Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences.	Hamidieh et. al (2013) [115]		May 1991 – Jun 2010	< 15	133	14	10.5	N/A	x
	Tehran	Case Series	Newly diagnosed AML at Hematology and Oncology Clinics of Vali-Asr and Ali-Asghar hospitals, affiliated to Tehran University of Medical Sciences and Iran University of Medical Sciences.	Memarian et. al (2007) [116]		N/A	0.33 – 21	14	3	21.4	N/A	x

d. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Africa and the Middle East

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL /AML (%)	Methods for APL Classification	
											Cytogeneticst (15;17)	Morphology (FAB)
Israel (8.1%)	N/A	Case Series	AML at Schneider Children's Medical Centre of Israel, Soroka Hospital and Kaplan Hospital; children with DS and non-Fanconi birth defects included.	Stark et. al (2004) [117]		Jul 1998 – Jan 2003	< 20	86	7	8.1	x	x
Oman (12.9%)	N/A	Case Series	Treated at Sultan Qaboos University Hospital, national referral center for pediatric leukemia.	al Lamki et. al (2004) [118]		Jan 1993 – Jan 2003	< 12	11	1	9.1	x	x
	Muscat	Case Series	Treated at Sultan Qaboos University Hospital, national referral center for pediatric leukemia; patients with s- AML, MDS excluded.	Udayakumar et. al (2007) [119]		Nov 2001 – Nov 2006	≤ 16	18	3	16.7	x	x
Saudi Arabia (3.4%)	N/A	Case Series	Primary treatment at King Faisal Specialist Hospital and Research Center.	Jenkin et al (2000) [120]		1983 – 1997	< 17	86	1	1.2	x	x
	Jeddah	Case Series	All children with AML diagnosed at King Abdulaziz	Khattab et. al (2008) [121]		Jan 1986 – Nov 2005	0.5 – 14	54	3	5.6	x	N/A

d. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Africa and the Middle East

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL /AML (%)	Methods for APL Classification: Cytogeneticst (15;17)	Methods for APL Classification: Morphology (FAB)
			Medical City.									
Turkey (8.8%)	N/A	Case Series	Diagnosed with AML at Cukurova University Medical School.	Komur et. al (2010) [122]		N/A	1 – 17	34	3	8.8	x	x

e. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Asia

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/ AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
Asia												
China (Mainland)	N/A	Case Series	N/A	Wang et. al (2012) [123]		Apr 2005 – Apr 2010	≤ 16	179	27	15.1	x	x
(19.3%)	N/A	Registry[a]	N/A	Zhang and Zhu (2012) [124]		1996 – 2004	N/A	141	51	36.2	x	x
	N/A	Case Series	Patients with cytotoxic chemotherapy, blastic transformation of CML, secondary malignancy or DS excluded.	Zhai et. al (2011) [125]		Aug 1994 – Dec 2008	< 18	68	12	17.6	x	x
	Beijing	Case Series	Newly diagnosed AML.	Shang et. al (1999) [126]		Nov 1992 – Mar 1997	N/A	15	2	13.3	N/A	x
	Guang zhou	Case Series	AML at the department of Pediatrics Nanfang Hospital.	Feng et. al (2014) [127]		Jan 2011 – Oct 2012	2 – 16	38	2	5.3	x	x

e. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Asia

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/ AML (%)	Methods for APL Classification	
											Cytogenetics t(15;17)	Morphology (FAB)
	Shanghai	Case Series	Patients with no-pretreatment included.	Tang et. al (2003) [128]		N/A	< 14	12	2	16.7	x	x
	Suzhou	Case Series	Patients at Children's Hospital of Soochow Unversity.	Yan-Fang et. al (2013) [129]		2000 – 2010	1 – 13	70	10	14.3	x	x
	Wuhan	Case Series	Newly diagnosed AML.	Jiang et. al (2014) [130]		Jan 2009 – Aug 2013	0.4 – 13	241	43	17.8	x	x
	Zhejiang	Case Series	AML at Children's Hospital of Zheijiang University School of Medicine.	Xu et. al (2010) [131]		Jan 1997 – Dec 2005	< 16	185	49	26.5	x	x
	Zheijang	Case Series	AML at First Affiliated Hospital, Zhejiang University College of Medicine, central hospital with more than 95% of patients residents of the province.	Cheng et. al (2009) [132]		Dec 1994 – Nov 2007	0 – 19	146	44	30.1	x	x
China (Hong Kong) (9.3%)	Hong Kong	Case Series	Consecutive cases at a regional Hong Kong hospital.	Chan et. al (2004) [133]		Dec 1996 – Dec 2003	0.67 – 16	43	4	9.3	x	x
China (Taiwan) (11.0%)	N/A	Clinical Trial	Diagnosed at Chang Gung Memorial Hospital and Mackay Memorial Hospital.	Liang et. al (2013) [134]	TPOG	Dec 1995 – Jun 2011	0 – 19.7	206	17	8.3	x	x

e. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Asia

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/ AML (%)	Methods for APL Classification	
											Cytogenetics t(15;17)	Morphology (FAB)
	N/A	Case Series	Treated at Mackay Memorial Hospital.	Yeh et. al (2007) [135]	TPOG	Nov 1995 – July 2004	< 15	48	6	12.5	x	x
	N/A	Clinical Trial	DS, systemic chloroma included; s-AML, MDS excluded.	Liang et. al (2006) [136]	TPOG	Jan 1997 – Dec 2002	0 – 17	243	24	9.9	x	x
	N/A	Case Series	Diagnosed at Mackay Memorial Hospital and Chang Gung Children's Hospital.	Liang et. al (2003) [137]	TPOG	N/A	≤ 18	91	12	13.2	x	x
India (8.8%)	Chandigarh	Case Series	Department of Hematology of Post Graduate Institute of Medical Education and Research (PGIMER) in Northern India.	Bhatia et. al (2012) [138]		Apr 2010 – Mar 2012	0.6 – 12	20	3	15.0	x	x
	New Delhi	Case Series	N/A	Agarwal et. al (2011) [139]		Jun 2004 – Dec 2008	1 – 18	80	1	1.3	x	x
	South India	Case Series	N/A	Mir Mazloumi et. al (2013) [140]		2009 – 2011	1 – 14	50	5	10.0	x	x
Indonesia (5.6%)	North Sumatra	Case Series	Patients at Subdivision of Pediatric Hematology, School of Medicine, University of North Sumatra /Dr. Pirngadi	Nasution et. al (1991) [141]		1983 – 1988	0 – 15	18	1	5.6	N/A	x

e. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Asia

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/ AML (%)	Methods for APL Classification	
											Cytogenetics t(15;17)	Morphology (FAB)
			Hospital Medan.									
Japan	N/A	Registry[a]	N/A	Horibe et. al (2013) [142]		2006 – 2010	< 20	891	70	7.9	N/A	x
(9.0%)	N/A	Clinical Trial	Newly diagnosed AML, DS included.	Shimada et al (2012) [143]	JCACSGAML 99	Jan 2000 – Dec 2002	0 – 15	318	32	10.1	x	x
	N/A	Case Series	AML from 4 centers.[b]	Ohta et. al (2011) [144]	JPLSG	1997 – 2007	N/A	375	42	11.2	N/A	x
	N/A	Case Series	N/A	Miyamura et. al (2004) [145]		Feb 1999 – May 2002	0.33 – 16	26[c]	3	11.5	x	x
	N/A	Case Series	Newly diagnosed AML.	Yamada et. al (2001) [146]		Jan 1988 – Feb 2000	0 – 16	159	7	4.4	x	x
	N/A	Clinical Trial	N/A	Iwai et. al (1999) [147]	CCLSG	N/A	N/A	94	9	9.6	x	x
	N/A	Case Series	Treated at Nagoya University Hospital and affiliates.	Kondo et. al (1999) 148]		1985 – 1997	0 – 16	64	3	4.7	N/A	x
	N/A	Case Series	Treated at Saitama Children's Medical Center.	Hayashi et. al (1991) [149]		Apr 1983 – Mar 1990	< 15	106	7	6.6	x	x
	Tokyo	Clinical Trial	Newly diagnosed AML from 40 participating institutions mainly located in Tokyo and suburbs, covering a	Tomizawa et. al (2007) [150]	TCC SG M91-13, M96-14	Aug 1991 – Sept 1998	2 – 15	216	14	6.5	x	x

e. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Asia

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/ AML (%)	Methods for APL Classification	
											Cytogenetics t(15;17)	Morphology (FAB)
			third to a fourth of Japanese pediatric population; patients with s-AML, MDS, death before therapy start, undifferentiated and mixed-lineage leukemia excluded.									
	Tokyo	Case Series	All new cases of leukemia at University of Tokyo Hospital or affiliated hospitals.	Bessho (1989)[d] [151]		1964 – 1976	N/A	36	2	5.6	N/A	x
						1977 – 1989	N/A	19	4	21.1	N/A	x
Malaysia (14.4%)	N/A	Case Series	AML at University Malaya Medical Centre, tertiary referral center for childhood cancer; patients with s-AML, MDS, or prior chemotherapy excluded; deceased and DS included.	Chan et. al (2004) [152]		May 1985 – Dec 1999	0 – 15	174	25	14.4	N/A	x
Nepal (20.0%)	Western Nepal	Case Series	Patients at the Manipal Teaching hospital in western Nepal.	Ghartimagar et. al (2012) [153]		Jan 2000 – June 2011	< 15	15	3	20.0	N/A	x
Pakistan (24.7%)	Islamabad	Case Series	Patients at Pakistan Institue of Medical Sciences;	Asif et. al (2011) [154]		Jul 2007 – Jul 2009	0.17 – 13	26	8	30.8	N/A	x

e. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Asia

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/ AML (%)	Methods for APL Classification	
											Cytogenetics t(15;17)	Morphology (FAB)
			patients already receiving cyotoxic therapy, already diagnosed with AML, CML, myeloproliferative disorders or MDS excluded.									
	Karachi	Case Series	N/A	Zaki et. al (2002) [155]		Jan 1987 – Aug 1997	< 14	23	10	43.5	N/A	x
	Karachi	Case Series	Patients at Aga Khan University Hospital, Karachi. Patients with hematological disorders (MDS, CML, aplastic anaemia), prior chemotherapy/ radiotherapy excluded. Not newly diagnosed cases with or without treatment, relapsed cases excluded.	Harani et. al (2005) [156]		Jan 1999 – Dec 2000	< 15	21	0	0.0	N/A	x
Singapore (10.6%)	N/A	Case Series	Treated at Children's Medical Institute, National University Hospital, deceased included.	Tan et. al (2007) [157]		Apr 1988 – Dec 2003	0.17 – 15	34	2	5.9	x	x

e. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Asia

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL/ AML (%)	Methods for APL Classification	
											Cytogenetics t(15;17)	Morphology (FAB)
	N/A	Case Series	Children treated at the National University of Singapore.	Quah et. al (1996) [158]		Jan 1988 – Jan 1994	< 12	13	2	15.4	N/A	x
South Korea (7.4%)	N/A	Case Series	AML at Samsung Medical Center.	Sung et. al (2007) [159]		July 2000 – Apr 2006	< 15	55	5	9.1	x	x
	Seoul	Case Series	Children with AL undergoing allogenic HCT at Asan Medical Center.	Lee et. al (2009) [160]		Jan 2000 – Apr 2007	0.6 – 15.4	35	2	5.7	x	N/A
Thailand (5.6%)	Bangkok	Case Series	Diagnosed with AL at Department of Pediatrics, Faculty of Medicine Rama Thibodi Hospital and Queen Sirikit National Institute of Child Health, Bangkok, Thailand.	Pakakasama et. al (2008) [161]		Jan 2004 – Dec 2006	0.83 – 13.2	20	1	5.0	x	x
	N/A	Case Series	Newly diagnosed AML at departments of Pediatrics, Srinakarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen and Faculty of Medicine, Ramathibodi Hospital,	Mukda et. al (2011) [162]		N/A	0.17 – 15	64	4	6.3	N/A	x

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e. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Asia

Region	Subregion	Source of Cases	Inclusion Criteria	Study (Year)	Study Series	Period of Data Collection	Age	AML	APL	APL/ AML	Methods for APL Classification	
(average %: APL/AML)								(n)	(n)	(%)	Cytogenetics t(15;17)	Morphology (FAB)
			Mahidol University, Bangkok, Thailand.									

f. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Oceania and Multinational Studies

Region	Subregion	Source of Cases	Inclusion Criteria	Study Author (Year)	Study Series	Period of Data Collection	Age	AML	APL	APL /AML	Methods for APL Classification	
(average %: APL/AML)								(n)	(n)	(%)	Cytogenetics t(15;17)	Morphology (FAB)
Oceania												
Australia (17.8%)	N/A	Clinical Trial	Previously untreated children with AML; DS and preleukemic myelodysplasia excluded.	Tiedemann et. al (1993) [163]		Nov 1984 – Jan 1991	0.25 – 16	31	4	12.9	x	x
	Melbourne	Case Series	Newly diagnosed AML at Royal Children's Hospital, Melbourne; patients too young for cytototoxic therapy or with death before treatment excluded.	Paton et. al (1982) [164]		Oct 1974 – Jan 1979	1 – 14.67	22	5	22.7	N/A	x
Multinational												

f. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Oceania and Multinational Studies

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study Author (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL /AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
North America (7.3%)	United States & Canada	Clinical Trial	CCG 213, children with acute monoblastic leukemia excluded.	Smith et. al (2005) [165]	CCG 251	Sept 1979 – Oct 1983	0 – 21	485	31	6.4	x	x
					CCG 213	May 1985 – Feb 1989	<21	532	50	9.4	x	x
			CCG 2891: children with previously untreated AML, acute undifferentiated or biphenotypic leukemia with evidence of myeloid differentiation, MDS or granulocytic sarcoma included.		CCG 2891	Oct 1989 – Apr 1995	<21	868	50	5.8	x	x
	United States & Canada	Case-Control	Newly diagnosed AML, telephone in residence of patient; biological mother of patient had to speak English and be avilable for interview.	Severson et. al (1993) [41]	CCG	Jan 1980 – Dec 1984	<18	187	14	7.5	N/A	x
Central America (14.6%)	El Salvador, Guatemala, Honduras	Case Series	Relapsed AML. Patients from Hospital Nacional de Ninos	Marjerrison et. al (2014) [166]		Sept 1997 – Apr 2011	<20	164	24	14.6	N/A	x

f. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Oceania and Multinational Studies

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study Author (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL /AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
			Benjamin Bloom in San Salvador, Unidad Nacional de Oncologia Pediatrica in Guatemala City, Hospital Escuela in Tegucigalpa and Hospital Rivas in San Pedro Sula; children with induction failure excluded.									
Europe	N/A	Clinical Trial	Patients with myelosarcoma, s-AML, MDS, DS or pre-treatment > 14 days excluded from analysis.	Creutzig et. al (2005)[a] [167]	BFM 83	Dec 1982 – Sept 1986	0 – 17	182	5	2.7	x	x
					BFM 87	Dec 1986 – Sept 1992	0 – 17	307	15	4.9	x	x
Europe	N/A	Registry[b]	Patients who underwent autologous HSCT for AML; DS patients excluded.	Locatelli et. al (2003)[a] [168]		Jan 1980 – Dec 1999	<16	387	36	9.3	x	x

f. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Oceania and Multinational Studies

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study Author (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL /AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
Europe	Austria, Czech Republic, Denmark, Finland, Germany, Iceland, Israel, Italy, Netherlands, Norway, Sweden, United Kingdom	Registry[b]	DS AML only.	Forestier et. al (2008)[a] [169]		1992 – 2005	0 – 12	189	5	2.6	x	x
Europe (6.0%)	Austria, Czech Republic, Germany, Switzerland	Clinical Trial	N/A	Creutzig et. al (2010) [170]	BFM-93,98,04	Sept 1993 – Dec 2007	0 – 18	1357	81	6.0	x	x
Europe	Austria, Denmark, England, Estonia, Finland, France, Iceland, Italy, Netherlands, Poland, Scotland, Slovakia, Slovenia, Spain, Sweden, Switzerland, Wales, West Germany	Registry	N/A	Gatta et. al (2001)[a] [171]	EUROCARE	1985 – 1989	<15	915	40	4.4	x	x
Europe (8.0%)	Czech Republic, France, Germany, Netherlands	Clinical Trial	N/A	Balgobind et. al (2011) [172]	DCOG, AML-BFM, CPH	N/A	N/A	237	19	8.0	x	x

f. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Oceania and Multinational Studies

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study Author (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL /AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
Europe (5.3%)	Denmark, Finland, Iceland, Norway, Sweden (Nordic Region)	Clinical Trial	Population based for children < 15; aged 15–18 patients were enrolled by local practice; patients treated with protocols outside of NOPHO-AML, pre-treated with costatic drugs for > 14 days, or with DS, Fanconi anemia, Kostmann syndrome, extramedullary myeloid tumor (without significant bone marrow involvement), t-AML excluded.	Molgaard-Hansen et. al (2010) [173]	NOPHO-AML 84,88,93	July 1984 – Dec 2003	0 – 18	525	28	5.3	x	x
Europe (6.1%)	Serbia, Montenegro[c]	Case Series	Newly diagnosed acute leukemia, in previously untreated patients at Mother and Child Health Institute of	Slavkovic et. al (2005) [174]		Oct 1996 – May 2002	0.33 – 17	33	2	6.1	x	x

f. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Oceania and Multinational Studies

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study Author (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL /AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
			Serbia, where 60 – 70% of childhood AL cases in region treated.									
Europe (4.2%)	Serbia, Montenegro, Slovenia, Croatia, Boznia and Herzegovina, Republic of Macedonia[c]	Case Series	N/A	Petkovic et. al (1992) [175]		N/A	0.5–15	24	1	4.2	x	x
Asia	China, Malaysia, India	Case Series	N/A	Leow et. al (2011)[a] [176]		N/A	0 – 17	150	18	12.0	x	x
Oceania (11.8%)	Australia, New Zealand	Clinical Trial	Previously untreated AML, patients with MDS, s-AML, DS-related leukemic disorders excluded, death before treatment excluded.	O'Brien et. al (2002) [177]	ANZCCSG	Dec 1986 – May 1999	<18	262	31	11.8	x	x
Multiregional	Australia, Canada,Puerto Rico, Switzerland, United States	Clinical Trial	Patients with APL (4), juvenile myelomonocytic leukemia, documented bone marrow failure syndromes, DS or secondary/ treatment	Cooper et. al (2012)[a] [178]	COG	Dec 2003 – Nov 2005	>1, ≤21	349	4	1.1	x	x

f. Geographic Distribution of De Novo Childhood APL Cases as a Percentage of AML in Oceania and Multinational Studies

Region (average %: APL/AML)	Subregion	Source of Cases	Inclusion Criteria	Study Author (Year)	Study Series	Period of Data Collection	Age	AML (n)	APL (n)	APL /AML (%)	Methods for APL Classification: Cytogenetics t(15;17)	Methods for APL Classification: Morphology (FAB)
			related leukemia not eligbile; patients with MDS not eligible unless they presented with karyotypic abnormalities characteristic of de novo AML.									
Multiregional	Australia, Europe, United States	Case Series	Patients with secondary leukemia and leukemic cells with abnormal karotype excluded.	Rowley et. al (1982)[a] [179]		N/A	0 – 19	56	2	3.6	x	x

AL, acute leukemia; ALL, acute lympocytic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CCG, Children's Cancer Group; COG, Children's Oncology Group; DS, Down syndrome; FAB, French-American-British; MDS, myelodysplastic syndrome; N/A, not available;s-AML, secondary AML; SJCRH, St. Jude Children's Research Hospital; TACL, Therapeautic Advances in Childhood Leukemia Consortium.

[a] National Cancer Registry

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BCSGIAL, Brazilian Collaborative Study Group of Infant Acute Leukemias; BCSGIL, Brazilian Cooperative Study Group of Infant Leukemia; CML, chronic myeloid leukemia; DS, Down syndrome; FAB, French-American-British; MDS, myelodysplastic syndrome; N/A, not available; PINDA, National Program for Antineoplastic Drugs for Children; s-AML, secondary AML.

[a] Children's Cancer Subregistry of Belarus, AEIOP National Registry, Childhood Cancer Registry of Piedmont, Zaragoza, Girona and Valencia Registries, National Registry of Childhood Tumors, respectively.

[b] Both cases of APL were classified of FAB M5, but showed t(11;17) cytogenetics characteristic of APL (FAB M3).

[c] Seven patients non M3 t-AML were excluded from original patient total of 140 for purposes of this analysis.

[d] Two non-M3 t-AML were excluded from original patient total of 28 for purposes of this analysis

[e] Centers: G. Gaslini Chidlren's Hospital, Genoa; Bambino Gesu Children's Hospital, Rome; Regina Marghertia-S. Anna Children's Hospital, Turin; Pediatric Clinic, Milano Bicocca University, Monza; Pediatric Hematology Oncology, Padua; Burlo Garofalo Children's Hospital, Trieste; Pediatric Clinic, University of Catania, Catania; A. Meyer Children's Hospital, Florence.

[f] 5 secondary AMLs, FAB types M5 (4) and M6 (1) were excluded from original patient total of 68 for purposes of this analysis.

[g] Two non-M3 secondary AMLs were excluded from original patient total of 84 for purposes of this analysis.

AEIOP, Associazione Italiana Ematologia Oncologia Pediatrica; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BFM, Berlin-Frankfurt-Münster; CML, chronic myeloid leukemia; DCLSG, Dutch Childhood Leukemia Study Group; DCOG, Dutch Childhood Oncology Group; DS, Down syndrome; EUROCARE, European Cancer Registry; FAB, French-American-British; HPOG, Hungarian Pediatric Oncology-Hematology Group; LAME, Leucémie Aiguë Myéloblastique Enfant; MDS, myelodysplastic syndrome; MRC, UK Medical Research Counci; N/A, not available; PPLLSG, Polish Pediatric Leukemia/Lymphoma Study Group; s-AML, secondary AML; SPOG, Swiss Paediatric Oncology Group; TMD, transient myeloproliferative disorder.

[a] Hospital-based registry at Children's Cancer Hospital Egypt

AL, acute leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; DS, Down syndrome; FAB, French-American-British; MDS, myelodysplastic syndrome; N/A, not available; s-AML, secondary AML.

[a] Registry of Hematology and Blood Diseases Hospital of Chinese Academy of Medical Sciences and Peking Union Medical College and the Japan Society of Pediatric Hematology, respectively.

[b] Centers: Department of Pediatrics and Developmental Science, Mie University Graduate School of Medicine; Department of Pediatrics, Osaka University; Center for Clinical Research, National Center for Child Health and Development; Department of Pediatrics, Aichi Medical University.

[c] Two non M3 secondary leukemias excluded for purposes of this analysis.

[d] Authors onducted a slide reclassification study (n=36) and a prospective study (n=19), both shown above.

AL, acute leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CCLSG, Children's Cancer and Leukemia Study Group; CML, chronic myeloid leukemia; DS, Down syndrome; FAB, French-American-British; HCT, hematopoietic stem cell transplantation; JCACSG, Japanese Childhood AML Cooperative Study Group-JPLSG, Japanse Pediatric Leukemia and Lymphoma Study Group; MDS, myelodysplastic syndrome; N/A, not available; s-AML, secondary AML; TCCSG, Tokyo Children's Cancer Study Group; TPOG, Taiwan Pediatric Oncology Group.

[a] Studies not represented in Figure 2 due to patient populations in large non-contiguous geographical regions.

[b] European Blood and Bone Marrow Transplantation Registry and International Berlin-Frankfurt-Munster Registry, respectively.

[c] Studies were conducted in nations formerly known as Serbia & Montenegro and Yugoslavia, respectively.

AL, acute leukemia; AML, acute myeloid leukemia; ANZCCSG, Australian and New Zealand Children's Cancer Study Group; APL, acute promyelocytic leukemia; BFM, Berlin-Frankfurt-Munster; CCG, Children's Cancer Study Group; COG, Children's Oncology Group; CPH, Czech Pediatric Hematology Working Group; DCOG, Dutch Childhood Oncology Group; DS, Down syndrome; FAB, French-American-British; HSCT, hematopoietic stem cell transplantationr; MDS, myelodysplastic syndrome; N/A, not available; NOPHO, Nordic Society of Paediatric Haematology and Oncology; s-AML, secondary AML; t-AML, therapy-related AML.

Table 3

Characteristics of Childhood t-APL Cases (n = 28) [a]

Characteristics	Mean	Median (Range)	No. (%)
Age at t-APL diagnosis (yrs)	11.4	10 (2 – 21)	
< 5			4 (14)
5 – 10			12 (43)
11 – 15			3 (11)
> 15			9 (32)
Sex			
Male			12 (43)
Female			16 (57)
Latency (mo)	35.8	32 (18 – 72)	**24** [b]
Cytogenetics			**26** [c]
t(15;17)			18 (69)
t(15;17) + others			4 (15)
t(5;17)			2 (8)
t(11;17)			1 (4)
Other			1 (4)
Primary Disease			
Hematological Diseases			**17 (61)**
Acute Lymphoblastic Leukemia			1 (4)
Hemophagocytic Lymphohistiocytosis			2 (7)
Hodgkin Lymphoma			4 (14)
Langerhans Cell Histiocytosis			7 (25)
Non-Hodgkin Lymphoma			3 (11)
Solid Tumors			**6 (21)**
Brain astrocytoma			1 (4)
Germ cell tumor (choriocarcinoma)			1 (4)
Glioblastoma			1 (4)
Neuroblastoma			1 (4)
Rhabdomyosarcoma			1 (4)
Wilms' Tumor			1 (4)
Other Conditions			**5 (18)**
Liver Transplant			2 (7)
Multiple Sclerosis			1 (4)
Psoriasis			2 (7)

Characteristics	Mean	Median (Range)	No. (%)
Treatment for Primary Disease [d]			
Radiation			9 (32)
Topoisomerase II inhibitors/anthracyclines [e]			27 (96)
Alkylating Agents [f]			14 (50)
Vinca Alkaloids [g]			12 (43)
Anti-metabolites [h]			8 (29)
Steroids [i]			8 (29)
Other [j]			9 (32)
Outcome			**19** [l]
Complete Remission			16 (84)
Death			3 (16)

[a] Ten additional cases of childhood t-APL were excluded due to cytogenetics inconsistent with APL or diagnosis by morphology alone.

[b] Latency information was not available for one case; three additional cases were excluded because the definition of latency used was not comparable to the rest of the cases.

[c] Cytogenetic information was not available for two cases. APL was confirmed by detection of PML-RARA using RT-PCR.

[d] Multiple types of drugs were involved in treatments for primary disease in many case studies. Drugs were counted in the table each time they were used.

[e] Topoisomerase II inhibitors/anthracyclines: actinomycin-D, doxorubicin/adriamycin, etoposide, mitoxantrone, teniposide, unspecified topoisomerase II inhibitors/anthracyclines.

[f] Alklayting agents: carboplatin, cisplatin, cyclophoshamide, dacarbazine, ifosfamide.

[g] Vinca alkaloids: vinblastine, vincristine/oncovin, vindesine.

[h] Antimetabolites: 6-mercaptopurine, azathioprine, cytarabine/cytosine arabinoside, methotrexate.

[i] Steroids: methylprednisone, prednisolone, prednisone, dexamethasone.

[j] Other: bleomycin, cyclosporine, tacrolimus, L-asparaginase.

[l] information on outcome was unavailable for 9 cases.

Table 4

Characteristics of Adult t-APL Cases (n = 260)

Characteristics	Range	No. (%)
Age Range (yrs)	21 – 81	
Sex		**248** [a]
Male		98 (39)
Female		150 (60)
Latency (mo)	1 – 276	
Primary Disease		
Hematological Diseases		**39 (15)**
AML/MDS		3 (1.1)
Diffuse large B-cell lymphoma		5 (1.9)
Follicular NHL		2 (0.8)
Folllicular lymphoma		3 (1.1)
HL		6 (2.3)
Mucosa-associated lymphoid tissue NHL		1 (0.4)
Multiple myeloma		1 (0.4)
NHL		11(4.2)
Primary-CNS NHL		1 (0.4)
SLL/CLL		4 (1.5)
T-cell NHL		1 (0.4)
Mantle cell lymphoma		1 (0.4)
Autoimmune Disorders		**4 (1.5)**
Chron's disease		1 (0.4)
Membranous glumerulonephropathy		1 (0.4)
Rhuematoid arthritis		2 (0.8)
CNS Disorders		**54 (21)**
Hydatiform mole		1 (0.4)
Lewis-Sumner Syndrome		1 (0.4)
Multiple sclerosis		51 (19.6)
Polyradiculoneuritis		1 (0.4)
Solid Tumors		**165 (63)**
Adenocarcinoma		1 (0.4)
Astrocytoma		1 (0.4)
Bladder carcinoma		2 (0.8)
Breast carcinoma		94 (36.2)
Cervical cancer		2 (0.8)
Choriocarcinoma		1 (0.4)
Colon cancer		6 (2.3)
Corpus-Uteri carcinoma		2 (0.8)

Characteristics	Range	No. (%)
Endometrium carcinoma		2 (0.8)
Gestational trophoblastic disease		1 (0.4)
Head and neck squamous cell carcinoma		2 (0.8)
Histiocytoma		1 (0.4)
Laryngeal carcinoma		2 (0.8)
Lung carcinoma		3 (1.1)
Malignant fibrous histiocytoma		2 (0.8)
Mixed germ cell tumor		1 (0.4)
Neuroectodermal tumor		1 (0.4)
Neuroepethlioma		1 (0.4)
Ovarian carcinoma		4 (1.5)
Pancreatic cancer		1 (0.4)
Primary location unknown carcinoma		1 (0.4)
Prostate carcinoma		21 (8.1)
Seminoma		2 (0.8)
Squamous cell carcinoma		2 (0.8)
Stomach cancer		1 (0.4)
Testicular cancer		4 (1.5)
Thyroid carcinoma		3 (1.1)
Tongue carcinoma		1 (0.4)
Other Conditions		**2 (0.8)**
Arthritis		1 (0.4)
Cardiac transplant		1 (0.4)
Treatment for Primary Disease[b]		
Radiation		153 (59)
Topoisomerase I inhibitors [c]		1 (0.4)
Topoisomerase II inhibitors/anthracyclines [d]		186 (72)
Alkylating agents [e]		146 (56)
Vinca alkaloids [f]		46 (18)
Antimetabolites [g]		101 (39)
Taxanes [h]		7 (3)
Steroids [i]		17 (7)
Monoclonal Antibodies [j]		6 (2)
Hormone Therapy [k]		10 (4)
Unspecified Chemotherapy		1 (0.4)
Other [l]		29 (11)

[a] Gender information not available for 12 cases.

[b] Multiple types of drugs were involved in treatments for primary disease in many case studies. Drugs were counted in the table each time they were used.

[c] Topoisomerase I inhibitors: irinotecan.

[d] Topoisomerase II inhibitors/anthracyclines: actinomycin-D, daunorubicin, doxorubicin/adriamycin, ellipticine, epirubicin, etoposide, hydroxydanunorubicin, idarubicin, mitoxantrone, teniposide, unspecified topoisomerase II inhibitors.

[e] Alklayting agents: busulfan, carboplatin, chlorambucil, cisplatin, cyclophoshamide, dacarbazine, ifosfamide, lomustin, mechlorethamine, melphalan, mitomycin, oxaliplatin, prednimustine, thiotepa, procarbazine, unspecified alkylating agents.

[f] Vinca alkaloids: vinblastine, vincristine/oncovin, vindesine, vinorelbine.

[g] Antimetabolites: 5-FU fluorouracil, 6-mercaptopurine, azathioprine, capacitabine, cytarabine/cytosine arabinoside, fludarabine, methotrexate, thioguanine, unspecified antimetabolite chemotherapy.

[h] Taxanes: docetaxel, paclitaxel, unspecified taxanesantimetabolite chemotherapy.

[i] Steroids: methylprednisone, prednisolone, prednisone, unspecified steroids.

[j] Monoclonal antibodies: herceptin, rituximab.

[k] Hormone therapy: anastrazole, leuprolide, medroxyprogesterone acetate, tamoxifen, unspecified hormone therapy.

[l] Other: bleomycin, immunospuression, interferon, interferon-beta, TNF-alpha inhibitor.

AML, acute myeloid leukemia; CNS, central nervous system; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia.

Table 5

Occupational, Environmental and Life-style Related Factors Associated with an Increased Risk of APL in Adults

a. Case-Control	Subgroup	OR (95% CI)	APL (n)	Control (n)	Reference
Occupational & Industrial					
Benzene		1.95 (0.98–3.88)	18	20	Wong et. al (2010) [254]
Metal work		14.00 (1.72–113.77)	7	1	Wong et. al (2010) [254]
Textile and other fabric manufacturing		2.5 (1.10–5.66)	15	14	Wong et. al (2010) [254]
General construction		2.28 (1.03–5.05)	15	15	Wong et. al (2010) [254]
Metals		2.28 (1.03–5.05)	10	8	Wong et. al (2010) [254]
Shoe making		6.3 (1.3–31.1)	2	17	Mele et. al (1995) [255]
Environmental & Lifestyle					
Smoking	ever smoking	0.32 (0.1–1) [a]	4	168	Bjork et. al (2001) [256]
	non-smoker		14	166	
	ever smoking	0.57 (0.32–1)	23	943	Moorman et. al (2002) [257]
	current smoking	0.47 (0.23–0.96)	11	461	
	past smoking	0.72 (0.35–1.49)	12	472	
		0.56 (0.30–1.03)	53	618	Sandler et. al (1993) [258]
Alcohol consumption		0.96 (0.68–1.69)	44	83	Wong et. al (2009) [259]
BMI	underweight	0.81 (0.35–1.85)	10	26	Wong et. al (2009) [b] [259]
	desirable	1.00 (reference)	65	149	
	overweight	1.55 (0.92–2.63)	30	60	
	obese	2.15 (0.89–5.20)	11	13	
Home/workplace renovation		2.02 (1.06–3.85)	20	21	Wong et. al (2009) [259]
		2.01 (1.01–4.00)	N/A	N/A	Wong et. al (2010) [254]
b. Case Series	**Subgroup**	**OR (95% CI)**	**APL**	**AML**	**References**
Occupational & Industrial			**(n)**	**(n)**	
Benzene			4	9	Travis et. al (1994) [260]
			1	20	Yin et. al (1989) [263]

a. Case-Control	Subgroup	OR (95% CI)	APL (n)	Control (n)	Reference
Electricians		4.4 (2.1–9.1) [c]	22	11	Pulsoni et. al (1998) [261]
Environmental & Lifestye			**BMI**	**BMI**	
BMI	25th %tile BMI		22.8	21.3	Estey et. al (1997) [d] [262]
	50th %tile BMI		26	24.2	
	75th %tile BMI		28.9	27.6	

[a] Odds ratio for ever smokers versus life-long non-smokers

[b] APL had a positive trend of OR by increasing BMI (p-trend = 0.03)

[c] Risk of APL versus other AML expressed as an OR.

[d] Wilcoxon Mann–Whitney test for hypothesis of no difference between distribution of BMI in APL and other AML patients, p=0.0003

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BMI, body mass index; CI, confidence interval; N/A, not available; OR, odds ratio.