Demographic and Prognostic Factors of 455 Patients with Acute Leukemia Admitted to Two Referral Hospitals in Tehran-Iran During Ten Years (2001-2011)

Parvin Ayremlou, Seyed Mohsen Razavi, Masoud Solaymani-Dodaran, Masoud Vakili, Mohsen Asadi-Lari

Abstract

Background: Global death toll of Acute Leukemia (AL), as a heterogeneous group of hematopoietic malignancies, is rather high, i.e. almost 74% of 300,000 new cases die every year. This reflects a poor prognosis of this malignancy in most parts of the world, where contemporary and rather complex remedies are not available. There are a few well documented reports about the epidemiologic features of AL at national level in Iran. This retrospective study demonstrates demographic and laboratory features of Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) patients admitted to the main referral oncology hospitals in the ex-Iran University of Medical Sciences in Tehran (Firoozgar and Rasoul-Akram hospitals) during the last decade (2001-2011).

Methods: Medical records of all patients admitted to the both hospitals diagnosed with AML and ALL were reviewed during the study period for demographic, biological and clinical characteristics at diagnosis.

Results: Four-hundred fifty five patients were diagnosed with AML and ALL, who admitted to the both hospitals during ten years, of whom 59.6% (271 patients) were male. Fifty five percent of patients had AML and 44.6% had ALL, both significantly dominated in men (p<0.001). AML patients died more significantly (p<0.05) and the most deaths occurred in older patients (p<0.001). Initial WBC count was significantly related to death (p= 0.001), where the least death (13%) occurred in the group with initial WBC between 5-10×10^3/μL and most of deceased had an initial WBC more than 10×10^3/μL. Logistic regression showed that age, fever and WBC were significant prognostic factors.

Conclusion: Demographic characteristics of AL patients were almost the same as other global reports. Most deaths occurred in older patients, those who had fever, and patients with higher WBC count at first admission, which warrants more investigations accurately and also improvements in hospital records.

Keywords: Acute Myeloid Leukemia; Acute Lymphoblastic Leukemia; Epidemiology; Iran

Introduction

Leukemias are heterogeneous group of hematopoietic malignancies that include diverse and biologically distinct sub-groups [1]. There are four major subtypes of leukemia in most cancer registries including Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Chronic Lymphoblastic Leukemia (CLL), and Chronic Myeloid Leukemia (CML) [2]. Acute leukemias afflict both adults and children while chronic leukemia involves adults mainly [1]. The American Cancer Society estimates that 31,500 individuals are diagnosed with one form of leukemia in the United States each year, of whom approximately 21,500 patients (68.2%) die from their disease [3], the recent cancer registry in Iran indicated that there were 4393 new cases of hematologic malignancies in 2008, of whom 805
cases (18.3%) had ALL and 432 cases (9.8%) had AML [4]. Although the incidence of acute leukemia accounts for less than 3% of all cancers, [5] but it is the leading cause of cancer death in children and younger individuals less than 39 years [3].

Acute Myeloid Leukemia (AML) occurs predominantly in adults [6-8], which afflicts the elderly more frequently than the young. Statistics show that more than half of patients with AML are older than 60 years, with a median age of 65 years for newly diagnosed patients [3-10]. Leukemia is the most common cancer and the most common cause of disease-related death in childhood [9,11]; ALL is the most common malignancy in children, accounting for 30% of all cancers in white population and 80% of all leukemias [12-14] , which predominates in males up to twice than female [15]. Leukemias share some major risk factors worldwide, particularly ionizing radiation, though the descriptive etiology of different types and subtypes of leukemias is not identical [1].

Although most patients achieve remission initially, but over 25% of patients will ultimately experience a relapse, and those patients with an early bone marrow relapse have less than 10% survival. Similarly, 50% of patients with AML will relapse [11]. Complete remission with standard induction chemotherapy for ALL patients is 70-90% [16, 17] and for patients with AML ranges from 60% to 80% [18, 19]. However, the majority of patients will relapse and die during 2 years after a remission[19]; so patients with relapse will have a poor prognosis [17, 20]. Statistics from 1996 to 2002 in the United States showed 5-year relative survival rates of 34.4% for adults aged 65 and 4.3% for older than 65 years [6].

A number of factors have been reported as affecting the outcome of the disease, including age, initial White Blood Cell (WBC) count, time to achieve complete remission, immunophenotype (T versus B cell), abnormal karyotypes and cytogenetics [21-23]. Several prognostic parameters have been identified in AML, where the most important factors with respect to survival rate are age and cytogenetics [24]. According to the most recent report of the national cancer registry of Iran in 2008, Age-Standardised incidence Rate (ASR) of leukemia in Iran and Tehran was 8.94 and 7.36 for men and 6.29 and 5.89 for women per 100,000 population, respectively [4]. Acute leukemia constitutes the majority of leukemia whereas about 71 % of lymphoblastic leukemia and 66 % of myeloblastic leukemias have been reported as acute in Tehran metropolitan area [25].

Many factors affect the prognosis of acute leukemia. Risk stratification helps the clinicians to select therapeutic modalities based on prognostic indicators, which has been emphasized in the National Cancer Institute/Rome criteria [26] including age, WBC count at diagnosis, immunophenotype [27] cytogenicity of the disease, [28] and brain status [29]. High WBC count at diagnosis has been

| Variable          | Type of diseases | P value |
|-------------------|------------------|---------|
| Gender            |                  |         |
| Male              | AML No. (%)      | 142 (56.3) |
|                   | ALL No. (%)      | 129 (63.5) |
| Female            | AML No. (%)      | 110 (43.7) |
|                   | ALL No. (%)      | 74 (36.5)  |
|                   | Odds Ratio= 0.74 |         |
| Age groups        |                  |         |
| ≤15               | AML No. (%)      | 5 (2) |
|                   | ALL No. (%)      | 54 (26.2) |
|                   | Odds Ratio= <0.001 | |
| >15               | AML No. (%)      | 129 (51.4) |
|                   | ALL No. (%)      | 129 (63.5) |
| Fever             |                  |         |
| No fever          | AML No. (%)      | 55 (24.3) |
|                   | ALL No. (%)      | 64 (35.8) |
|                   | Odds Ratio= 0.012 |         |
|                   |                  |         |
| Hb (g/dl)         |                  |         |
| <5                | AML No. (%)      | 12 (4.8)  |
|                   | ALL No. (%)      | 9 (4.5)  |
|                   | Odds Ratio= 0.394 |         |
| 5-10              | AML No. (%)      | 173 (68.9) |
|                   | ALL No. (%)      | 126 (63.3) |
| >10               | AML No. (%)      | 66 (26.3)  |
|                   | ALL No. (%)      | 64 (32.2)  |
| PLT (×10³/μL)     |                  |         |
| <50               | AML No. (%)      | 158 (62.9) |
|                   | ALL No. (%)      | 98 (49.2)  |
|                   | Odds Ratio= 0.004 |         |
| 50-100            | AML No. (%)      | 47 (18.7)  |
|                   | ALL No. (%)      | 38 (19.2)  |
| >100-150          | AML No. (%)      | 18 (7.2)   |
|                   | ALL No. (%)      | 18 (9.0)   |
| >150              | AML No. (%)      | 28 (11.2)  |
|                   | ALL No. (%)      | 45 (22.6)  |
| WBC (×10³/μL)     |                  |         |
| <5                | AML No. (%)      | 98 (39)    |
|                   | ALL No. (%)      | 101 (50.7) |
|                   | Odds Ratio= 0.031 |         |
| 5-10              | AML No. (%)      | 36 (14.4)  |
|                   | ALL No. (%)      | 28 (14.1)  |
| >10               | AML No. (%)      | 117 (46.6) |
|                   | ALL No. (%)      | 70 (35.2)  |
Demographic and Prognostic Factors of 455 Patients With Acute Leukemia…

Table 2. Different Variables Among Deceased AL Patients (n=210)

| Variable          | Sub-groups | Deceased (%) | P value |
|-------------------|------------|--------------|---------|
| Gender            | Male       | 121 (57.6)   | 0.44    |
|                   | Female     | 89 (42.4)    |         |
| Type of leukemia  | AML        | 128 (61)     | 0.03    |
|                   | ALL        | 82 (39)      |         |
| Age groups        | ≤15        | 13 (6.2)     | <0.001  |
|                   | 15-45      | 122 (58.4)   |         |
|                   | ≥45        | 47 (35.4)    |         |
| Medical Centers   | Firoozgar  | 124 (59)     | 0.17    |
|                   | Rasol-Akram| 86 (41)      |         |
| Fever             | No fever   | 45 (23.6)    | 0.015   |
|                   | fever      | 146 (76.4)   |         |
| Hb (g/dl)         | <5         | 10 (4.8)     | 0.9     |
|                   | 5-10       | 136 (65.4)   |         |
|                   | >10        | 62 (29.8)    |         |
| PLT (×10^3/μL)    | <50        | 129 (62.3)   | 0.1     |
|                   | 50-100     | 38 (18.4)    |         |
|                   | 100-150    | 14 (6.8)     |         |
|                   | >150       | 26 (12.6)    |         |
| WBC (×10^3/μL)    | <5         | 72 (34.8)    | 0.001   |
|                   | 5-10       | 31 (15)      |         |
|                   | >10        | 104 (50.2)   |         |

Table 3. Logistic Regression of Prognostic Factors

| Variable          | Sub-groups | OR   | 95% CI | P value |
|-------------------|------------|------|--------|---------|
| Gender            | Male       | Ref  | -      | -       |
|                   | Female     | 0.75 | 0.5-1.1| 0.2     |
| Type of leukemia  | AML        | Ref  | -      | -       |
|                   | ALL        | 0.97 | 0.6-1.6| 0.92    |
| Age groups        | ≤15        | Ref  | -      | -       |
|                   | 15-45      | 0.4  | 0.2-0.9| 0.02    |
|                   | ≥45        | 0.26 | 0.1-0.64| 0.004  |
| Medical Centers   | Firoozgar  | Ref  | -      | -       |
|                   | Rasol-Akram| 0.95 | 0.6-1.5| 0.82    |
| Fever             | No fever   | Ref  | -      | -       |
|                   | fever      | 0.58 | 0.3-0.94| 0.03    |
| Hb (g/dl)         | <5         | Ref  | -      | -       |
|                   | 5-10       | 1.03 | 0.4-2.7| 0.96    |
|                   | >10        | 0.7  | 0.3-1.9| 0.51    |
| PLT (×10^3/μL)    | <50        | Ref  | -      | -       |
|                   | 50-100     | 1.34 | 0.8-2.3| 0.28    |
|                   | 100-150    | 1.53 | 0.7-3.4| 0.29    |
|                   | >150       | 1.7  | 0.9-3.2| 0.1     |
| WBC (×10^3/μL)    | <5         | Ref  | -      | -       |
|                   | 5-10       | 0.58 | 0.3-1.1| 0.08    |
|                   | >10        | 0.5  | 0.3-0.78| 0.003   |

considered as a strong prognostic factor for treatment failure, resistance and recurrence [30].
Materials and Methods

All patients diagnosed with AML and ALL admitted to the two major oncology referral hospitals of ex-Iran University of Medical Sciences (Firoozgar and Rasoul-Akram Hospitals) were included in this retrospective study during the last decade from March 2001 to March 2011. Prognostic factors which were considered in the analysis included demographic, biological and clinical characteristics at diagnosis. Gender, age, type of leukemia, White Blood Cells (WBC), Hemoglobin (Hb), Platelet count (PLT) and fever (axillary>37.5°C) were taken from the medical records to fill a pre-determined checklist. Phone calls were made to spot patients’ death.

Data were analysed by SPSS v.17 software. Patients’ variables were summarized by frequency tabulation (for categorical variables) or by calculating mean and median for continuous variables. Univariate analysis of the association between each variable and outcome was done using chi-square method. Logistic regression was conducted to find out the most significant prognostic factors.

Results

Demographic features of the patients are shown in Tables 1-2. Four-hundred fifty five patients were diagnosed with AML and ALL, of whom 253 cases were admitted in Firoozgar (55.6%) and 202 cases (44.4%) in Rasoul-Akram Hospitals. Almost 60% (271 patients) were male, 55.4 % of patients had AML and 44.6 % had ALL, both significantly dominated in men i.e. 56.3 % male versus 43.7 % female for AML and 63.5% male versus 36.5% female for ALL. Totally, the mean age at diagnosis was 35.58. The mean age in AML was 44.79 and in ALL was 24.20 years. Most patients (56.8%) were in the age group of 15-45 years, while the younger group (≤15 years) was in the minority (13%). AML was the most common in older people and ALL in youngsters (p<=<0.001). AML patients tended to be admitted more in Firoozgar Hospital (p=0.01), while equal number of patients were admitted to both hospitals during the study period. Most of AML (64%) and ALL (75%) patients had fever. Most of AML and ALL patients had PLT less than 50000/μL. The proportion of AML patients who had WBC higher than 10000/μL, was more than ALL patients, while patients with less than 5000/μL were more likely to be AML. There was no significant gender difference in the age, fever and hematologic features.

Amongst 455 patients, 130 deaths were recorded in both hospitals, while the remaining patients were followed by telephone calls. Wrong telephone numbers, vacant or unavailable contact numbers were excluded and amongst 325 patients after follow up, 80 deaths were detected. Survival analysis was performed for 210 patients, of whom 128 patients (61%) had AML and 82 (39%) had ALL. Amongst them 74% survived one year and 26% survived more than 1 year (Results are not shown here).

The relationship between death and AL variables are shown in Table 2. AML patients died significantly more than ALL patients (p<0.05). Compared with patients under 15 years, most deaths occurred in older patients (p<0.001). There was no significant relationship between death and hematoglobin and platelet levels, however most deaths occurred in patients with fever (p =0.01) and high initial WBC count i.e. more than 10×103/μL which was significantly related to death (p= 0.001), while the least death (13%) occurred in the group with initial WBC of 5-10×109/μL. Logistic regression showed that age, fever and WBC count were significant prognostic factors (Table 3).

Discussion

Research on epidemiological features of acute leukemia is poorly reported in Iran [36]. This study demonstrates demographic characteristics of a large number of patients with AML and ALL admitted to two hematology-oncology wards during 10 years. Leukemia is moderately common and accounts for almost 3 percent of all cancers in both developed and developing countries [5]. Demographic features in this retrospective study were consistent with other studies, where men were affected more with acute leukemia, [37, 38] ALL occurs more in children under 15 years [12] and AML occurs more in elderly [3, 7, 39, 40]. In this study, 26.7% of AML patients were older than 60 years while only 2% were less than 15
years; also 26.6% of ALL patients were less than 15 years while 3.4% were older than 60 years.

Our results showed that males were more diagnosed with acute leukemia, which is in compliance with other studies [1, 10, 41-43]. Incidence rates are usually higher in males [1]. Kobayashi et al reported 72.4% male dominancy in AML [42], and Santos et al reported that 62% of AML patients were men [44]. ALL is the most common cancer in children and adolescents, [13, 40] representing almost one-third of all form of cancer during childhood in white population [1], whereas AML is presented mainly in adults [7]. Our findings indicated that 46.6% of AML patients were over 45 years while 9.9% of ALL patients were in this age group, and only 2% of AML patients were less than 15 years.

The mean age at diagnosis for AML and ALL patients were 44.79 and 24.20, respectively, which were less than Giles et al report for AML patients (50 years) [20], however, almost similar age distributions have been reported in Iran [45] and elsewhere [11, 46]. In the current study, the mean survival rates in total, AML, and ALL patients were 290.7, 280.9 and 303.5 days, respectively. Most deaths occurred in AML patients because age is an important factor in the prognosis of acute leukemia [24, 47] and also the mean age in ALL is less than AML patients. Among studied factors (age, gender, duration of fever, Hb, WBC and PLT) age, fever, and WBC were associated significantly with death. Most deaths occurred in the elderly, patients with fever and those with higher WBC counts at diagnosis, which are in compliance with the body of literature [9, 10, 16, 31, 32, 34]. Although the most employed cut point for initial WBC count are $50 \times 10^3/\mu L$ [13, 27, 48-52] and $10 \times 10^3/\mu L$ [53-56], but other cut points close to this study (<5, 5-10 >10 $\times 10^3/\mu L$) are well accepted in the literature [16, 33]. Yanada et al found that in a series of T-ALL adults, patients with initial WBC count of $3.5 \times 10^3/\mu L$ had longer survival rates than others [16].

This retrospective descriptive study suffers from a number of limitations. First of all, our findings are limited to the two hospitals during the last ten years, secondly, contact details were not available for most of the patients and medical and laboratory records were not complete and last but not the least, the difference in classification might be a source of bias similar to other studies. A population-based study is required to determine an accurate estimation of epidemiological characteristics of acute leukemia. However, our results indicate significant differences between the types of leukemia and demographic, laboratory and clinical features, particularly duration of fever and WBC counts, which warrant further analysis and more studies in stylish design. Simple laboratory tests such as CBC with differentiation (for the purpose of absolute lymphocyte count) are probably more efficient in risk stratification of AL patients [26].

In conclusion, this retrospective study reveals that demographic characteristics of AL patients admitted to the selected referral hospitals in Tehran were almost the same as other global reports. Most deaths occurred in older patients, those who had fever and finally patients with higher WBC count at diagnosis. The prognostic factors need more investigations to find out their influence accurately. Complete hospital records, setting up hospital or population-based registry and more advanced study designs are required to provide better healthcare for acute leukemia patients.

Acknowledgment
This research was conducted as part of the first author’s M.Sc dissertation, which was funded by School of Public Health at TUMS. Authors are thankful to the medical records departments at Firrozgar and Rasul Akram Hospitals for their kind supports and patience, and also to those families who provided necessary information about the survival of their beloved patients during the data collection.

Conflict of Interest
The authors have no conflict of interest in this article.

Authors’ Contribution
Parvin Ayremlou collected and analyzed the data and drafted the manuscript in Farsi, Seyed Mohsen Razavi, Masoud Vakili, had visited all the patients as oncologists and also contributed in designing and implementing the study, Masoud Salaymani-Dodaran and Mohsen Asadi-Lari contributed in designing and conducting the study, supported data collection and proof read the manuscript. Mohsen Asadi-Lari was the main supervisor and wrote the paper.

References
1. Petridou E, Pourtsidis A, Trichopoulos D. Leukemias. In: Adami H, Hunter D, Trichopoulos D, editors. Textbook of Cancer Epidemiology. Oxford: Oxford University Press; 2008.
2. Xie Y, Davies SM, Xiang Y, Robison LL, Ross JA. Trends in leukemia incidence and survival in the United States (1973–1998). Cancer. 2003;97(9):2229-35.
3. Deschler B, Lübbert M. Acute myeloid leukemia: Epidemiology and etiology. Cancer. 2006;107(9):2099-107.

4. Iran CDC. Iran Cancer Registration Report, 2008. Tehran: Ministry of Health and Medical Education, Centre for Disease Control; 2011 Contract No.: Document Number.

5. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74-108.

6. Klepin HD, Balducci L. Acute Myelogenous Leukemia in Older Adults. The Oncologist. 2009;14(3):222-32.

7. Lang K, Earle CC, Foster T, Dixon D, Van Gool R, Menzin J. Trends in the treatment of acute myeloid leukemia in the elderly. Drugs Aging. 2005;22(11):943-55.

8. Creutzig U, Büchner T, Sauerland MC, Zimmermann M, Reinhardt D, Döhner H, et al. Significance of age in acute myeloid leukemia patients younger than 30 years. Cancer. 2008;112(3):562-71.

9. Wheatley K, Brookes CL, Howman AJ, Goldstone AH, Milligan DW, Prentice AG, et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. British Journal of Haematology. 2009;145(5):598-605.

10. Chen CC. Pretreatment prognostic factors and treatment outcome in elderly patients with de novo acute myeloid leukemia. Annals of Oncology. 2005;16(8):1366-73.

11. De Angulo G, Yuen C, Palla SL, Anderson PM, Zweidler-McKay PA. Absolute lymphocyte count is a novel prognostic indicator in ALL and AML. Cancer. 2008;112(2):407-15.

12. Feltbower RG, McNally RJQ, Kinsey SE, Lewis IJ, Picton SV, Proctor SJ, et al. Epidemiology of leukaemia and lymphoma in children and young adults from the north of England, 1990–2002. European Journal of Cancer. 2009;45(3):420-7.

13. Goyon P, Qu RP, Chappell RJ, Willoughby ML, Tubergen DG, Steinherz PG, et al. Survival after relapse in childhood acute lymphoblastic leukaemia: impact of site and time to first relapse--the Children's Cancer Group Experience. Cancer. 1998;82(7):1387-95.

14. Laks D, Longhi F, Wagner MB, Garcia PC. [Survival evaluation of children with acute lymphoblastic leukaemia treated with Berlin-Frankfurt-Munich trial]. J Pediatr (Rio J). 2003;79(2):149-58.

15. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. Blood. 2012;119(1):34-43.

16. Yanada M, Jinmai I, Takeuchi J, Ueda T, Miyawaki S, Tsuzuki M, et al. Clinical features and outcome of T-lineage acute lymphoblastic leukemia in adults: A low initial white blood cell count, as well as a high count predict decreased survival rates. Leukemia Research. 2007;31(7):907-14.

17. von Stackelberg A, Völzke E, Kühl J-S, Seeger K, Schrauder A, Escherich G, et al. Outcome of children and adolescents with relapsed acute lymphoblastic leukaemia and non-response to salvage protocol therapy: A retrospective analysis of the ALL-REZ BFM Study Group. European Journal of Cancer. 2011;47(1):90-7.

18. Tavernier E, Le QH, Elhamri M, Thomas X. Salvage therapy in refractory acute myeloid leukaemia: prediction of outcome based on analysis of prognostic factors. Leuk Res. 2003;27(3):205-14.

19. Shipley JL, Butera JN. Acute myelogenous leukemia. Experimental Hematology. 2009;37(6):649-58.

20. Giles F, O'Brien S, Cortes J, Verstovsek S, Bueso-Ramos C, Shan J, et al. Outcome of patients with acute myelogenous leukaemia after second salvage therapy. Cancer. 2005;104(3):547-54.

21. Wells RJ, Arthur DC, Srivastava A, Heerema NA, Le Beau M, Alonzo TA, et al. Prognostic variables in newly diagnosed children and adolescents with acute myeloid leukaemia: Children's Cancer Group Study 213. Leukemia. 2002;16(4):601-7.

22. Horibe K, Hara J, Yagi K, Tawa A, Komada Y, Oda M, et al. Prognostic factors in childhood acute lymphoblastic leukaemia in Japan. Japan Association of Childhood Leukemia Study. Int J Hematol. 2000;72(1):61-8.

23. Hilden JM. Analysis of prognostic factors of acute lymphoblastic leukaemia in infants: report on CCG 1953 from the Children's Oncology Group. Blood. 2006;108(2):441-51.

24. Schoch C, Kern W, Schnittger S, Büchner T, Hiddemann W, Haferlach T. The influence of age on prognosis of de novo acute myeloid leukaemia differs according to cytogentic subgroups. Haematologica. 2004;89(9):1082-90.

25. Mohagheghi MA, Mosavi-Jarrah A, Malekzadeh R, Parkin M. Cancer incidence in Tehran metropolis: the first report from the Tehran Population-based Cancer Registry, 1998-2001. Arch Iran Med. 2009;12(1):15-23.

26. De Angulo G, Yuen C, Palla SL, Anderson PM, Zweidler-McKay PA. Absolute lymphocyte count is a novel prognostic indicator in ALL and AML: implications for risk stratification and future studies. Cancer. 2008;112(2):407-15.

27. Chang H, Salma F, Yi Q-L, Patterson B, Brien B, Minden MD. Prognostic relevance of immunophenotyping in 379 patients with acute myeloid leukaemia. Leukemia Research. 2004;28(1):43-8.

28. Cavalli F. Textbook of Medical Oncology. Third ed. London; 2004.

29. Smith M, Arthur D, Camitta B, Carroll AJ, Crist W, Goyon P, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukaemia. J Clin Oncol. 1996;14(1):18-24.

30. Vaitkeviciene G, Forestier E, Hellebostad M, Heyman M, Jonsson OG, Lahneemaki PM, et al. High white blood cell count at diagnosis of childhood acute lymphoblastic leukaemia: biological background and prognostic impact. Results from the NOPHO ALL-92 and ALL-2000 studies. Eur J Haematol. 2011;86(1):38-46.

31. Carroll WL, Raetz EA. Clinical and Laboratory Biology of Childhood Acute Lymphoblastic Leukemia. The Journal of Pediatrics. 2012;160(1):10-8.
32. Shaikh MU, Ali N, Adil SN, Khurshid M. Outcome of adult patients with acute lymphoblastic leukaemia receiving the MRC UKALL XII protocol: a tertiary care centre experience. Singapore Med J. 2011;52(5):370-4.

33. Thomas X. Outcome of Treatment in Adults With Acute Lymphoblastic Leukemia: Analysis of the LALA-94 Trial. Journal of Clinical Oncology. 2004;22(20):4075-86.

34. de Jonge HJM, Valk PJM, de Bent ESJM, Schuringa JJ, Ossenkoppele G, Vellenga E, et al. Prognostic impact of white blood cell count in intermediate risk acute myeloid leukemia: relevance of mutated NPM1 and FLT3-ITD. Haematologica. 2011;96(9):1310-7.

35. Plasschaert SLA, Kamps WA, Vellenga E, de Vries EGE, de Bent ESJM. Prognosis in childhood and adult acute lymphoblastic leukaemia: a question of maturation? Cancer Treatment Reviews. 2004;30(1):37-51.

36. Ziaei JE. High frequency of acute promyelocytic leukemia in northwest Iran. Asian Pac J Cancer Prev. 2004; 5(2):188-9.

37. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. Blood. 2011;119(1):34-43.

38. Koh H, Nakamae H, Hagihara K, Nakane T, Manabe M, Hayashi Y, et al. Factors that contribute to long-term survival in patients with leukemia not in remission at allageneic hematopoietic cell transplantation. Journal of Experimental & Clinical Cancer Research. 2011;30(1):36.

39. Pulsoni A, Pagano L, Latagliala R, Casini M, Cerri R, Crugnola M, et al. Survival of elderly patients with acute myeloid leukemia. Haematologica. 2004;89(3):296-302.

40. Hijjya N, Hudson MM, Lensing S, Zacher M, Onciu M, Behm FG, et al. Cumulative Incidence of Secondary Neoplasms as a First Event After Childhood Acute Lymphoblastic Leukemia. JAMA: The Journal of the American Medical Association. 2007;297(11):1207-15.

41. Beltran B, Quiñones P, Morales D, Cotrina E, Castillo JJ. Different prognostic factors for survival in acute and lymphomatous adult T-cell leukemia/lymphoma. Leukemia Research. 2011;35(3):334-9.

42. Kobayashi H, Matsuyama T, Ueda M, Suzuki T, Ozaki K, Mori M, et al. Predictive Factors of Response and Survival following Conventional Treatment in Acute Myeloid Leukemia Progression from Myelodysplastic Syndrome. Internal Medicine. 2009;48(18):1629-33.

43. Santos FP, Faderl S, Garcia-Manero G, Koller C, Beran M, O’Brien S, et al. Adult acute erythroleukemia: an analysis of 91 patients treated at a single institution. Leukemia. 2009;23(12):2275-80.

44. Santos FP, Faderl S, Garcia-Manero G, Koller C, Beran M, O’Brien S, et al. Adult acute erythroleukemia: an analysis of 91 patients treated at a single institution. Leukemia. 2009;23(12):2275-80.

45. Sayehmiri K, Eshraghian MR, Mohammad K, Alimoghaddam K, Foroushani A, Zeraati H, et al. Prognostic factors of survival time after hematopoietic stem cell transplant in acute lymphoblastic leukemia patients: Cox proportional hazard versus accelerated failure time models. Journal of Experimental & Clinical Cancer Research. 2008;27(1):74.

46. Annino L. Treatment of adult acute lymphoblastic leukaemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. Blood. 2002;99(3):863-71.

47. Rabe C, Mey U, Paaschau M, Musch A, Tasci S, Glasmacher A, et al. Outcome of patients with acute myeloid leukemia and pulmonary infiltrates requiring invasive mechanical ventilation—a retrospective analysis. Journal of Critical Care. 2004;19(1):29-35.

48. Emerenciano M, Menezes J, Vasquez ML, Zalcberg I, Thuler LCS, Pombo-de-Oliveira MS. Clinical relevance ofFLT3 gene abnormalities in Brazilian patients with infant leukemia. Leukemia & Lymphoma. 2008;49(12):2291-7.

49. Khalid S, Moiz B, Adil SN, Khurshid M. Retrospective review of pediatric patients with acute lymphoblastic leukemia: a single center experience. Indian J Pathol Microbiol. 2010;53(4):704-10.

50. Malufuson JV, Etienne A, Turlure P, de Revel T, Thomas X, Contentin N, et al. Risk factors and decision criteria for intensive chemotherapy in older patients with acute myeloid leukemia. Haematologica. 2008;93(12):1806-13.

51. Oliveira LCO, Romano LGM, Prado-Junior BPA, Covas DT, Rego EM, De Santos GC. Outcome of acute myeloid leukemia patients with hyperleukocytosis in Brazil. Medical Oncology. 2009;27(4):1254-9.

52. Trigg ME, Sather HN, Reaman GH, Tubergen DG, Steinherz PG, Gaynon PS, et al. Ten-year survival of children with acute lymphoblastic leukemia: A report from the Children’s Oncology Group. Leukemia & Lymphoma. 2008;49(6):1142-54.

53. Anderson JE. Outcome after induction chemotherapy for older patients with acute myeloid leukemia is not improved with mitoxantrone and etoposide compared to cytarabine and daunorubicin: a Southwest Oncology Group study. Blood. 2002;100(12):3869-76.

54. Bonilla M, Gupta S, Vasquez R, Fuentes SL, deReyes G, Ribeiro R, et al. Predictors of outcome and methodological issues in children with acute lymphoblastic leukaemia in El Salvador. European Journal of Cancer. 2010;46(18):3280-6.

55. Pulsoni A, Iacobelli S, Bernardi M, Borgia M, Camera A, Cantore N, et al. M4 acute myeloid leukemia: the role of eosinophilia and cytogenetics in treatment response and survival. The GIMEMA experience. Haematologica. 2008;93(7):1025-32.

56. Wahlin A. Improved outcome in adult acute myeloid leukemia is almost entirely restricted to young patients and associated with stem cell transplantation. Eur J Haematol 2002;68:54-63.