Determining the Significant Prognostic Factors for the Recurrence of Pediatric Acute Lymphoblastic Leukemia Using a Competing Risks Approach

Anahita Saeedi1, MSc; Ahmadreza Baghestani2, PhD; Aliakbar Khadem Maboudi3, PhD; Hamid Farhangi4, MD

1Department of Biostatistics, School of Paramedical Sciences, Shahid Beheshti University, Tehran, Iran; 2Physiotherapy Research Center, Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; 3Department of Biostatistics, School of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; 4Department of Pediatrics Hematology and Oncology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence:
Ahmadreza, Baghestani, PhD; Department of Biostatistics, School of Paramedical Sciences, Qods Square, Tajrish, Postal code: 16616-84433, Tehran, Iran
Tel: +98 9121711548
Fax: +98 21 22707347
Email: Baghestani.ar@gmail.com
Received: 31 August 2019
Revised: 20 October 2019
Accepted: 24 November 2019

Abstract

Acute lymphoblastic leukemia (ALL) is the most common cause of cancer-related fatality among children. This study aimed to identify the significant prognostic factors for the incidence of pediatric ALL. This retrospective study, conducted from 2007 to 2016 in the Iranian city of Mashhad, enrolled 417 patients with ALL. The diagnosis was confirmed by Giemsa staining of bone marrow smears. The first recurrence was regarded as the event of interest and non-relapse mortality as the competing event through a three-parameter Gompertz model. The level of statistical significance for univariate and multivariate analyses was set at 0.2 and 0.05, respectively. The first recurrence occurred in 44 (10.6%) survivors. Disease-free survival and 5-year overall survival rates were 85.9% and 74%, correspondingly. The five-year incidence rate for the first recurrence was 11.5% in the presence of non-relapse mortality. Briefly, the characteristics of the Gompertz model conferred more effective prognostic factors. Age above 10 years (P=0.010), involvement of the central nervous system (P=0.050), a high white blood cell count (P=0.020), and tumor lysis syndrome (P=0.010) were the significant prognostic factors for the recurrence and mortality of ALL. Accordingly, careful monitoring in the administration of treatment protocols is suggested to reduce the risk of recurrence and death in these patients.

Keywords
● Survival analyses
● Lymphoblastic leukemia
● Acute
● Childhood
● Competing risks

Introduction

Acute lymphoblastic leukemia (ALL) is common cancer among children and the most common cause of death from cancer before age 20. Over the past few decades, the treatment of childhood leukemia has been highly successful, with the cure rate of ALL rising to 90%. An improved remission rate of 90% for childhood ALL in the last 40 years has been achieved with optimized chemotherapy. The incidence of ALL is highest among children between the ages of one and four years. Recent studies have shown an increase in ALL incidence among males of all ages. The survival rate of pediatric ALL has progressed to nearly 90% within the past decades. This improvement is
chiefly because of the adoption of changes in the treatment based on each patients’ pharmacodynamics and pharmacogenomics, as well as augmented supportive care. Additionally, biomedical technology has ushered in striking advancements in treatment.2, 6

Survival analysis incorporates situations where the person under study may experience multivariate competing events, which calls for competing risk models as the best way to estimate the survival time.7

In this study, we sought to determine the significant prognostic factors for the recurrence of pediatric ALL by considering the first recurrence in children with ALL to be the event of interest and non-relapse mortality to be the competing event.

### Patients and Methods

The present retrospective study was performed on patients aged below 15 years who were treated for ALL at Sheikh Hospital in the Iranian city of Mashhad between March 2007 and February 2016. The inclusion criterion permitted the inclusion of pediatric patients with ALL, and the exclusion criteria were age above 15 years and ALL with mature B-cell origins.

Our center is a university-affiliated teaching hospital in a metropolitan area. During the study period, the initial review was carried out on 600 patients, of whom 183 were excluded on grounds of duplicate or incomplete clinical records. The data set for the analysis was extracted from the patients’ clinical records. The study protocol was approved by the institutional ethics committee (approval code: Ir.sbmu.retech.rec.1397.652), and informed consent was obtained from the parents/custodians of all the patients.

ALL diagnosis was first confirmed by the presence of at least 25% lymphoblasts through the Giemsa staining of the study population's bone marrow smears. ALL with B-cell origins and ALL with T-cell origins were differentiated using flow cytometry. Complete remission was defined as the absence of blast cells in the cerebrospinal fluid, fewer than 5% blast cells in bone marrow, and complete progression of clinical symptoms. Complete remission was confirmed via microscopy.

In this center, ALL treatment is based on the Berlin-Frankfurt-Münster protocol, modified at the discretion of the treating physician to accommodate patients’ physical condition and response to treatment.

Data on the study population’s demographic characteristics, laboratory results, and treatment methods were obtained from medical records.

Clinical characteristics were used as prognostic variables in the analysis. The cut-point value for platelet count was based on the normal range defined in a study by Daly.8

In the presence of competing events, the Kaplan–Meier analysis will yield biased results, hence the use of other tools for estimating survival in such situations. One such tool is the cumulative incidence function.

The data were analyzed with a parametric competing risks model. A three-parameter Gompertz model was used because of its distribution flexibility in that it factors in both the event of interest and the competing event, simultaneously. Our primary outcome measure was which prognostic factors were significantly associated with the first recurrence of pediatric ALL. Variables with significance levels of less than 0.2 in the univariate analysis were re-assessed in the multivariate model. A stepwise procedure called “forward selection” was applied to include all the eligible variables based on the Akaike Information Criterion.9

The statistical analyses were carried out using SAS, version 9.4 (SAS Institute Inc, Cary, NC, USA). The level of statistical significance for the univariate and multivariate analyses was set at 20% and 0.05%, respectively.

### Results

Our study population was comprised of 417 patients with ALL aged between nine months and 17 years at the time of diagnosis. The mean age was 5.5±3.7 years for males and 5.63±3.9 years for female subjects. The majority of the patients (72.7%) did not experience either event (death or recurrence) during the study period. Seventy (16.8%) patients died before the first recurrence. Among survivors, the first recurrence happened in 44 (10.6%) patients. The disease-free survival and five-year overall survival rates were 85.9% and 74%, respectively. Most of the patients were treated with the Berlin-Frankfurt-Münster protocol. The demographic and clinical features of the patients are presented in Table 1, which shows the classification of the patients into subgroups according to the cutoff value of each factor cited.

A cumulative incidence curve was plotted for the event of interest and the competing event (Figure 1). The cumulative incidence probabilities at one, two, three, and five years are illustrated in the graph. For the first recurrence, the two-year cumulative incidence probability was 4.9. Therefore, the cumulative incidence (marginal probability) for leukemia recurrence within two years, in the presence of non-relapse mortality,
Table 1: Demographic and prognostic factors of the children with acute lymphoblastic leukemia

| Variable                  | Group      | N (%)  |
|---------------------------|------------|--------|
| Age (y)                   |            |        |
| <1                        | 35 (8.39)  |        |
| 1-10                      | 322 (77.23)|        |
| >10                       | 60 (14.38) |        |
| Gender                    |            |        |
| Male                      | 169 (40.53)|        |
| Female                    | 248 (59.47)|        |
| WBC (cells/mL)            |            |        |
| <10000                    | 254 (60.91)|        |
| 10000-49999               | 101 (24.22)|        |
| 50000-99999               | 27 (6.47)  |        |
| ≥100000                   | 35 (8.40)  |        |
| Hemoglobin (g/dL)         |            |        |
| <8                        | 191 (45.80)|        |
| ≥8                        | 226 (54.20)|        |
| PLT (cells/mL)            |            |        |
| <150000                   | 331 (79.37)|        |
| 150000-400000             | 71 (17.04) |        |
| >400000                   | 15 (3.59)  |        |
| Cell lineage              |            |        |
| T cell                    | 29 (6.95)  |        |
| B cell                    | 388 (93.05)|        |
| CNS involvement           |            |        |
| Yes                       | 13 (3.11)  |        |
| No                        | 404 (96.89)|        |
| Intracranial hemorrhage   |            |        |
| Yes                       | 58 (13.90) |        |
| No                        | 359 (86.10)|        |
| Mediastinal mass          |            |        |
| Yes                       | 2 (0.47)   |        |
| No                        | 415 (99.53)|        |
| Rheumatoid signs          |            |        |
| Yes                       | 130 (31.17)|        |
| No                        | 287 (68.83)|        |
| Tumor lysis syndrome      |            |        |
| Yes                       | 21 (5.03)  |        |
| No                        | 396 (94.97)|        |
| Hepatosplenomegaly        |            |        |
| Yes                       | 175 (41.96)|        |
| No                        | 242 (58.04)|        |
| Lymphadenopathy           |            |        |
| Yes                       | 86 (20.62) |        |
| No                        | 331 (79.38)|        |

WBC, White blood cell; PLT, Platelet; CNS, Central nervous system

Figure 1: The figure shows the cumulative incidence curve of both the event of interest and the competing event. The cumulative incidence probability for the first recurrence was higher than that for non-relapse mortality.
was 4.9%. For non-relapse mortality, the two-year cumulative incidence probability was 12.9; thus, the incidence (marginal probability) of non-relapse mortality in the presence of the first recurrence was 12.9% (Figure 1).

The results of the univariate and multivariate analyses are shown in Table 2. Based on the univariate model, a hemoglobin level of higher than 8 g/dL was associated with the first recurrence (P=0.059), whereas intracranial hemorrhage and lymphadenopathy were associated with non-relapse mortality (P=0.078, P=0.092). Also according to the univariate analysis, both the first recurrence and non-relapse mortality were associated with age at diagnosis of between 1 and 10 years and above 10 years (P=0.010, P=0.003), a white blood cell (WBC) count of higher than 50000 cells/mL (P<0.001, P<0.001), a platelet count of lower than 150 000 cells/mL (P<0.001, P<0.001), the involvement of the central nervous system (CNS) (P=0.121, P=0.049), and tumor lysis syndrome (TLS) (P=0.006, P=0.001). The multivariate model, conducted through stepwise regression, revealed a significant association between the first recurrence and age at diagnosis of above 10 years (P=0.010) and CNS involvement (P=0.050), as well as a significant association between non-relapse mortality and a WBC count of between 50 000 and 99 999 cells/mL (P=0.020). Also based on the multivariate analysis, Tumor lysis syndrome (TLS) was significant for both the event of interest and the competing event (P=0.010, P=0.004). Further, the risk of recurrence in patients older than 10 years was 60% higher than that in other age groups, patients with CNS involvement had twice the risk of recurrence than those without it, and patients who developed TLS were at 2.35 times greater risk of recurrence and 4.62 times higher risk of death than those who did not.

**Discussion**

The results of our final model, run on 417 patients with ALL aged between nine months and 17 years at diagnosis, revealed that the first recurrence was associated with older age.

| Table 2: Univariate and multivariate competing risks models of 417 cases of acute lymphoblastic leukemia |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable        | Event           | Group           | Univariate      | Multivariate    | Univariate      | Multivariate    |
|                 |                 | Hazard ratio    | SEM (80% CI)    | P value         | Hazard ratio    | SEM (80% CI)    | P value         |
| Age (y)         | First recurrence| <1              |                 |                 | 1.73            |                 |                 |
|                 |                 | 1-10            | 9.76            | 0.885           | 0.010*          | 1.55            | 0.379           | 0.277 |
|                 |                 | >10             | 1.73            | 0.184           | 0.003*          | 1.60            | 0.185           | 0.010** |
| Non-relapse mortality | 1-10 | 0.005 | 0.547 | 0.08-0.01 | <0.001* |
|                 |                 | >10             | 1.30            | 0.368           | 0.478 |
| Gender          | First recurrence| Male            | 0.93            | 0.126           | 0.601 |
|                 |                 | Female          |                 |                 |                 |                 |                 |
|                 | Non-relapse mortality | Male      | 1.00            | 0.336           | 0.977 |
|                 |                 | Female          |                 |                 |                 |                 |                 |
| WBC count (cells/mL) | First recurrence | <10000 | - | - | - |
|                 |                 | 10000-49999     | 0.86            | 0.144           | 0.329 |
|                 |                 | 50000-99999     | 0.09            | 0.359           | <0.001* |
|                 |                 | ≥100000         | 1.91            | 0.516           | 0.208* |
| Non-relapse mortality | <10000 | 0.86 | 0.421 | 0.50-1.48 | 0.724 | 0.97 | 0.533 | 0.42-2.22 | 0.944 |
|                 |                 | 10000-49999     | 0.641           | 0.306-1.587     | <0.001* |
|                 |                 | ≥100000         | 1.78            | 0.441           | 0.191* |

*P < 0.05, **P < 0.01*
| Variable                  | Event             | Group                      | Univariate |          |          | Multivariate |          |          |
|--------------------------|-------------------|----------------------------|------------|----------|----------|--------------|----------|----------|
|                         |                   | Hazard ratio               | SEM (80% CI) | P value  | Hazard ratio | SEM (80% CI) | P value  |          |
| Hemoglobin (g/dL)        | First recurrence  | >8                         | 0.79        | 0.124    | (0.67-0.92) | 0.059*       |          |          |
|                         |                   | ≤8                         | -           | -        | -          | -            | -        | -        |
|                         | Non-relapse       | >8                         | 1.41        | 0.342    | (0.90-2.19) | 0.315        |          |          |
|                         | mortality         | ≤8                         | -           | -        | -          | -            | -        | -        |
| PLT count (cells/mL)     | First recurrence  | <150000                    | 17.1        | 0.249    | (12.46-23.6) | <0.001*      |          |          |
|                         |                   | 150000-400000              | -           | -        | -          | -            | -        | -        |
|                         |                   | >400000                    | 0.85        | 0.819    | (0.29-2.44) | 0.846        |          |          |
|                         | Non-relapse       | <150000                    | 0.01        | 0.467    | (0.00-0.03) | <0.001*      |          |          |
|                         | mortality         | 150000-400000              | -           | -        | -          | -            | -        | -        |
|                         |                   | >400000                    | 0.06        | 2.65     | (0.00-2.03) | 0.309        |          |          |
| Cell lineage             | First recurrence  | T-cell                     | 0.92        | 0.251    | (0.56-1.51) | 0.757        |          |          |
|                         |                   | B-cell                     | -           | -        | -          | -            | -        | -        |
|                         |                   | Non-relapse                | T-cell      | 1.23     | 0.671      | (0.33-4.63)  | 0.749    |          |
|                         | mortality         | B-cell                     | -           | -        | -          | -            | -        | -        |
| CNS involvement          | First recurrence  | Yes                        | 5.43        | 1.092    | (1.33-22.08) | 0.121*       | 2.04     | 0.385    |
|                         |                   | No                         | -           | -        | -          | -            | -        |          |
|                         | Non-relapse       | Yes                        | 3.52        | 0.640    | (1.55-8.02) | 0.049*       | -        | -        |
|                         | mortality         | No                         | -           | -        | -          | -            | -        | -        |
| Intracranial hemorrhage  | First recurrence  | Yes                        | 1.20        | 0.181    | (0.95-1.52) | 0.297        |          |          |
|                         |                   | No                         | -           | -        | -          | -            | -        | -        |
|                         | Non-relapse       | Yes                        | 2.18        | 0.443    | (0.26-0.80) | 0.078*       | -        | -        |
|                         | mortality         | No                         | -           | -        | -          | -            | -        | -        |
| Rheumatoid signs         | First recurrence  | Yes                        | 0.85        | 0.133    | (0.65-1.10) | 0.232        |          |          |
|                         |                   | No                         | -           | -        | -          | -            | -        | -        |
|                         | Non-relapse       | Yes                        | 1.21        | 0.357    | (0.60-2.46) | 0.580        | -        | -        |
|                         | mortality         | No                         | -           | -        | -          | -            | -        | -        |
| Tumor lysis syndrome     | First recurrence  | Yes                        | 2.55        | 0.345    | (1.29-5.05) | 0.006*       | 2.35     | 0.349    |
|                         |                   | No                         | -           | -        | -          | -            | -        |          |
|                         | Non-relapse       | Yes                        | 5.17        | 0.499    | (1.93-13.81) | 0.001*       | 4.62     | 0.532    |
|                         | mortality         | No                         | -           | -        | -          | -            | -        |          |
| Hepatosplenomegaly       | First recurrence  | Yes                        | 1.01        | 0.124    | (0.79-1.29) | 0.910        |          |          |
|                         |                   | No                         | -           | -        | -          | -            | -        | -        |
|                         | Non-relapse       | Yes                        | 1.18        | 0.322    | (0.62-2.22) | 0.607        |          |          |
|                         | mortality         | No                         | -           | -        | -          | -            | -        | -        |
| Lymphadenopathy          | First recurrence  | Yes                        | 1.13        | 0.148    | (0.94-1.37) | 0.381        |          |          |
|                         |                   | No                         | -           | -        | -          | -            | -        | -        |
|                         | Non-relapse       | Yes                        | 1.81        | 0.354    | (1.15-2.86) | 0.092*       |          |          |
|                         | mortality         | No                         | -           | -        | -          | -            | -        | -        |

*Significant at 0.20, **Significant at 0.05, WBC, White blood cell; PLT, Platelet; CNS, Central nervous system
Survival of patients with ALL using a three-parameter Gompertz model

at diagnosis and CNS involvement, non-relapse mortality was associated with a high WBC count, and TLS was significant for both the event of interest and the competing event.

In the present study, a high WBC count was a strong prognostic factor for the incidence of non-relapse mortality. Our findings come into a sharper focus when considering the current dearth of data on the clinical and epidemiological aspects of ALL in children and adolescents as well as the risk factors for their response to treatment and survival. In a multivariate analysis by Patel and others, a WBC count of higher than 12,000 cells/mL emerged as a significant factor for lower rates of event-free survival and overall survival. A WBC count at diagnosis of higher than 500,000 cells/mL might be indicative of bulky tumor masses, mediastinal enlargement, huge lymphadenopathy, and hepatosplenomegaly, all of which are associated with a poor for ALL. WBC at diagnosis may be symptomatic of more bone marrow involvement and is accompanied by a severely suppressed immune system due to blast crisis (blast KRY-sis) and ineffective cells.

CNS involvement in this study was positively associated with the first recurrence. Conversely, in a multivariate analysis using Cox regression, Marwaha and others found that CNS involvement reduced the survival of their patients with ALL. CNS involvement is not associated with an increase in the risk of relapse in some studies; however, in the presence of blast crisis, CNS involvement at diagnosis is associated with worse event-free survival.

TLS was significant for mortality and the first recurrence in our investigation. In a study by Alakel and others, TLS was strongly associated with mortality. TLS occurs mostly in hematopoietic malignancies that are fast-growing and highly metabolic and have chemotherapy-sensitive cells like ALL. TLS is associated with a rise in the levels of phosphorus, potassium, calcium, and uric acid. This shift overcomes the homeostatic mechanisms, leading to acute renal failure, cardiac arrest, and death. The clinical consequences of TLS are serious: not only is TLS allied to cardiac, intestinal, and renal complications but also it lessens the effectiveness of curative treatments. All these scenarios together can result in the poor prognosis of TLS in children.

In our study, age above 10 years was associated with an increased risk of the first recurrence. Hossain and others explored the impact of age at diagnosis on mortality and reported a significant association to the degree that as children who were older at the time of diagnosis were at progressively higher chance of mortality. Apropos of age, various studies have shown that infants less than one year of age and children aged above nine years have a worse prognosis.

This study was performed in a specific geographical area of Iran, and there might be some genetic or environmental factors unbeknownst to us influencing the results and reducing their generalizability to other populations. Additionally, the fact that the data were collected by various healthcare providers potentially renders their documentation subject to inconsistency. Still, death and cancer recurrence are objective measures.

Conclusion

In light of the results of the current study, we conclude that older age, TLS, CNS involvement, and a high WBC count should be deemed high-risk indicators of ALL because they are adverse prognostic factors for its first recurrence and non-relapse mortality. Thus, we recommend that not only the administration of treatment protocols be monitored carefully to reduce the risk of death but also the WBC count be controlled closely to decrease the risk of relapse in this group of patients. TLS is strongly associated with both relapse and mortality in as much as it lessens the efficacy of cancer therapies; it should, therefore, be accorded sufficient attention in treatment plans.

Acknowledgments

This article was derived from a thesis by Anahita Saeedi from Shahid Beheshti University of Medical Sciences (research number: 14595). We thank the Pediatric Hematology and Oncology Group of Mashhad University of Medical Sciences for the provision of the information needed for this research.

Conflict of Interest: None declared.

References

1. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. N Engl J Med. 2015;373:1541-52. doi: 10.1056/NEJMra1400972. PubMed PMID: 26465987.
2. Pui CH, Mullighan CG, Evans WE, Relling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood. 2012;120:1165-74. doi: 10.1182/blood-2012-05-378943. PubMed PMID: 22730540; PubMed Central PMCID: PMC3418713.
3. Siegel RL, Miller KD, Jemal A. Cancer
statistics, 2019. CA Cancer J Clin. 2019;69:7-34. doi: 10.3322/caac.21551. PubMed PMID: 30620402.
4 Katz AJ, Chia VM, Schoonen WM, Kelsh MA. Acute lymphoblastic leukemia: an assessment of international incidence, survival, and disease burden. Cancer Causes Control. 2015;26:1627-42. doi: 10.1007/s10552-015-0657-6. PubMed PMID: 26376890.
5 Williams LA, Richardson M, Marcotte EL, Poynter JN, Spector LG. Sex ratio among childhood cancers by single year of age. Pediatr Blood Cancer. 2019;66:e27620. doi: 10.1002/pbc.27620. PubMed PMID: 30815990; PubMed Central PMCID: PMCPMC6472964.
6 Lustosa de Sousa DW, de Almeida Ferreira FV, Cavalcante Felix FH, de Oliveira Lopes MV. Acute lymphoblastic leukemia in children and adolescents: prognostic factors and analysis of survival. Rev Bras Hematol Hemoter. 2015;37:223-9. doi: 10.1016/j.bjhh.2015.03.009. PubMed PMID: 26190424; PubMed Central PMCID: PMCPMC4519710.
7 Kleinbaum DG, Klein M. Competing risks survival analysis. New York: Survival Analysis, Springer; 2012. p. 425-95.
8 Daly ME. Determinants of platelet count in humans. Haematologica. 2011;96:10-3. doi: 10.3324/haematol.2010.035287. PubMed PMID: 21193429; PubMed Central PMCID: PMCPMC3012758.
9 Zhang Z. Variable selection with stepwise and best subset approaches. Ann Transl Med. 2016;4:136. doi: 10.21037/atm.2016.03.35. PubMed PMID: 27162786; PubMed Central PMCID: PMCPMC4842399.
10 Patel A, Tiwari A, Biswas B, Chand Sharma M, Vishnubhatla S, Bakhshi S. Clinical Predictors and Prognostic Model for Pediatric Lymphoblastic Lymphoma Treated With Uniform BFM90 Protocol: A Single-Center Experience of 65 Patients From Asia. Clin Lymphoma Myeloma Leuk. 2019;19:e291-e8. doi: 10.1016/j.clml.2019.01.008. PubMed PMID: 30905539.
11 Marwaha RK, Kulkarni KP, Bansal D, Trehan A. Central nervous system involvement at presentation in childhood acute lymphoblastic leukemia: management experience and lessons. Leuk Lymphoma. 2010;51:261-8. doi: 10.3109/10428190903470323. PubMed PMID: 20038226.
12 Munch V, Trentin L, Herzig J, Demir S, Seyfried F, Kraus JM, et al. Central nervous system involvement in acute lymphoblastic leukemia is mediated by vascular endothelial growth factor. Blood. 2017;130:643-54. doi: 10.1182/blood-2017-03-769315. PubMed PMID: 28550041.
13 Alakel N, Middeke JM, Schetelig J, Bornhauser M. Prevention and treatment of tumor lysis syndrome, and the efficacy and role of rasburicase. Onco Targets Ther. 2017;10:597-605. doi: 10.2147/OTT.S103864. PubMed PMID: 28203093; PubMed Central PMCID: PMCPMC5295804.
14 Criscuolo M, Fianchi L, Dragonetti G, Pagano L. Tumor lysis syndrome: review of pathogenesis, risk factors and management of a medical emergency. Expert Rev Hematol. 2016;9:197-208. doi: 10.1586/17474086.2016.1127156. PubMed PMID: 26629730.
15 Hossain MJ, Xie L, McCahan SM. Characterization of pediatric acute lymphoblastic leukemia survival patterns by age at diagnosis. J Cancer Epidemiol. 2014;2014:865979. doi: 10.1155/2014/865979. PubMed PMID: 25309596; PubMed Central PMCID: PMCPMC4182848.