

Standard Computer Programs in Statistical Analysis of Survival in Childhood Lymphoblastic Leukemia

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ABSTRACT

A material comprising all children in Sweden with acute lymphoblastic leukemia diagnosed in the years 1973-80 was analysed statistically.

The total number of children was 505. Studies were made of 38 different variables, using frequency tables, cross tables, life table studies (1) and linear regression analysis according to Cox's method (2,4).

Chi-square tests and log rank tests were included in the methods. The combination of life-table studies and linear regression analysis proved to be of value in assessing the significance of different parameters and treatment programs with regard to prognosis.

The aim of this paper is to present a method for analysis of a patient material with use of standard computer programs. The results of the total analysis will be published elsewhere (3).

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a malignant disease which can occur in children of all ages. With regard to age, white blood cell count (WBC) at diagnosis and the presence or absence of central nervous system (CNS) involvement and/or of a mediastinal tumor at diagnosis, the children were classified as suffering from "high-risk leukemia" or "standard-risk leukemia" (3).

The children first received induction treatment for six weeks and if this was successful they were classified as being in complete remission. When remission was not achieved, the children died as a result of the disease and/or the treatment.

After remission, prophylactic radiation of the CNS was given, followed by maintenance therapy. Therapy was discontinued after

1. Identification variables at diagnosis

Name, month and year of birth, age, sex, hospital, home county, municipality and parish, date of diagnosis, presence or absence of CNS leukemia or mediastinal tumor, WBC, immunological classification, risk group, dominating symptom at diagnosis.

2. Therapy

Type of induction therapy, consolidation therapy, CNS prophylaxis therapy, and maintenance therapy, and their side effects. Treatment program.

3. Treatment results (time variables in months)

a) Duration of first remission

TCCR = Time in CCR, i.e. length of time from achieved remission to death during remission or to first relapse or to close date.

Every child with achieved remission had a value of one month or more for this variable. If the child died during induction the value was 00.

ACCR = Alive in CCR, i.e. length of time from achieved remission to close date. Only children who were in CCR at the close date had a value for this variable.

TCCR-OFFTHER = Time in CCR OFF THERAPY, i.e. length of time from discontinuation of therapy to death during remission or to first relapse or to close date. Every child with discontinuation of therapy after 3 years in CCR had a value for this variable.

ACCR-OFFTHER = Alive in CCR OFF THERAPY, i.e. length of time from discontinuation of therapy to close date. Only children who were in CCR at the close date had a value for this variable.

b) Patients alive at close date but after relapse

AREL-ONTHER-REM = Alive after RELapsing ON THERAPY, i.e. length of time from achieved remission to close date for children relapsing during therapy.

AREL-ONTHER-RELAPSE = Alive after RELapsing ON THERAPY, i.e. length of time from first relapse to close date for children relapsing during therapy.

AREL-OFFTHER-REM = Alive after RELapsing OFF THERAPY, i.e. length of time from achieved remission to close date for children relapsing after discontinuation of therapy.

AREL-OFFTHER-RELAPSE = Alive after RELapsing OFF THERAPY, i.e. length of time from first relapse to close date for children relapsing after discontinuation of therapy.

c) Dead patients

DCCR = Died during CCR, i.e. length of time from achieved remission

to death during CCR.

DREL-ON THER = Died after RELapsing ON THERAPY, i.e. length of time from achieved remission to death for children relapsing during therapy.

DREL-OFF THER = Died after RELapsing OFF THERAPY, i.e. length of time from achieved remission to death for children relapsing after discontinuation of therapy.

4. Other variables

REL₁ = Location of first relapse during therapy.

REL₂ = Location of second relapse during therapy.

REL-OFF THER = Location of first relapse after discontinuation of therapy.

CDCCR = Cause of death during CCR (e.g. infection).

TREL₁-REL₂ = Length of time in months between first and second relapse.

Measurements on the 38 variables for the 505 children constituted the data set.

The data set

In order to minimize the coding errors, a thorough examination of the data set comprising the following three steps was made:

- the data set was printed and compared with the medical records,
- frequency tables were used for checking missing values and outliers,
- cross tabulation was done to check that categorical responses were correctly classified.

Life tables and survival functions

In the commonly used method, with for example 5-year survival, information about patients participating in the study for a shorter time than five years would not be utilized. The proportion of patients surviving 5 years would in this case be:

$$P_5 = \frac{\text{Number of patients alive after five years in the study}}{\text{Number of patients participating in the study for at least five years}}$$

The life table technique, on the other hand, utilizes more information by computing this proportion as a cumulative proportion of surviving children. In principle this can be written as follows:

$$P_{1-5} = P_1 \times P_2 \times P_3 \times P_4 \times P_5$$

where p_1 is the proportion surviving one year, p_2 the proportion surviving two years provided that the patients survived the first year, and so on. This technique also provides a good idea of the

course of the disease. The problem with different starting and follow-up times is solved by rescaling the time variables so that all the patients start at time 0.

The end point can be one of the following:

- 1) Dead (response), i.e. died during CCR or relapse.
- 2) Withdrawn, i.e. alive in CCR at the end of the study (close date).
- 3) Lost, i.e. patients lost at follow-up.

The hazard and the density function are two ways of getting ideas of parametric models describing the survival time.

The hazard function (failure rate), λ_i is defined as:

$$\lambda_i = \frac{2 q_i}{h_i (1 + p_i)}$$

where

q_i = probability of dying in interval i

$p_i = 1 - q_i$

h_i = the width of the i 'th interval.

The density function (probability of death or relapse per unit time), f_i , is defined as:

$$f_i = \frac{P_i - P_{i+1}}{h_i} = \frac{P_i q_i}{h_i}$$

where

p_i = the estimate of the cumulative proportion, surviving to the beginning of the i 'th interval.

The density is sometimes called the curve of death and is in fact an absolute instantaneous rate of death or relapse.

The standard errors computed for the survival, hazard and density functions are used for computing confidence intervals and performing tests.

Tables 1 and 2 and Figure 2 show the computer print out of the life table and survival analysis from the program BMDP, P1L, 1977 (1).

RESULTS

Table 1. Example of survival analysis for female patients with achieved remission (computer print out).

LIFE TABLE AND SURVIVAL ANALYSIS. TIME VARIABLE IS TIDICCR. GROUPING VARIABLE IS KON. LEVEL IS F:

INTERVAL	ENTERED	WITHDRAWN	LOST	DEAD	EXPOSED	PROPORTION DEAD	PROPORTION SURVIVING	CUMULATIVE SURVIVAL	HAZARD (S.E.)	DENSITY (S.E.)
0.0-6.27	216	24	0	11	204.0	0.0539	0.9461	1.0000 0.0	0.0088 0.0027	0.0086 0.0000
6.27-12.53	181	10	0	13	176.0	0.0739	0.9261	0.9461 0.0158	0.0122 0.0034	0.0112 0.0000
12.53-18.80	158	10	0	21	153.0	0.1373	0.8627	0.8762 0.0237	0.0235 0.0051	0.0192 0.0000
18.80-25.07	127	11	0	20	121.5	0.1646	0.8354	0.7559 0.0318	0.0286 0.0064	0.0199 0.0000
25.07-31.33	96	8	0	8	92.0	0.0870	0.9130	0.6315 0.0368	0.0145 0.0051	0.0088 0.0000
31.33-37.60	80	9	0	4	75.5	0.0530	0.9470	0.5766 0.0384	0.0087 0.0043	0.0049 0.0000
37.60-43.87	67	9	0	5	62.5	0.0800	0.9200	0.5460 0.0393	0.0133 0.0059	0.0070 0.0000
43.87-50.13	53	9	0	4	48.5	0.0825	0.9175	0.5024 0.0407	0.0137 0.0069	0.0066 0.0000
50.13-56.40	40	8	0	1	36.0	0.0278	0.9722	0.4609 0.0423	0.0045 0.0045	0.0020 0.0000
56.40-62.67	31	8	0	1	27.60	0.0370	0.9630	0.4481 0.0430	0.0060 0.0060	0.0026 0.0000
62.67-68.93	22	4	0	0	20.0	0.0	1.0000	0.4315 0.0445	0.0 0.0	0.0 0.0
68.93-75.20	18	5	0	0	15.5	0.0	1.0000	0.4315 0.0445	0.0 0.0	0.0 0.0
75.20-81.47	13	4	0	0	11.0	0.0	1.0000	0.4315 0.0445	0.0 0.0	0.0 0.0
81.47-87.73	9	2	0	0	8.0	0.0	1.0000	0.4315 0.0445	0.0 0.0	0.0 0.0
87.73-94.00	7	7	0	0	3.5	0.0	1.0000	0.4315 0.0445	0.0 0.0	0.0 0.0
QUANTILE	ESTIMATE	STANDARD ERROR								
75TH	19.10	2.28								
MEDIAN (50TH)	44.22	10.86								

Explanations of the table head:

TIME VARIABLE IS TIDICCR = Time from onset to response or close date.

KON = Sex; LEVEL IS F = Sex is female.

INTERVAL = Time in months in CCR.

ENTERED = Number of patients with a time in CCR corresponding to the interval in question.

DEAD = Number of patients responding in the interval in question, i.e. patients dying or relapsing in the interval.

The important function values in Table 1 are the CUMULATIVE SURVIVAL, which forms the basis of the survival curves in Figure 2.

The table also gives the median estimate in the material, i.e. the time in months when half the patients have responded.

Table 2 gives a summary of the analyses presented in Table 1 for female and male patients separately. The test statistics in Table 2 represent the results of two non-parametric rank tests for compar-

ison of the cumulative survival functions. The low p values indicate a difference between the two survival functions.

Table 2. Table summarizing the survival analyses. Test statistics for comparing the proportions of females and males in CCR.

SUMMARY TABLE				
	TOTAL	DEAD	CENSORED	PERCENT CENSORED
F	216	88	128	0.5926
M	264	146	118	0.4470
	----	----	----	
TOTALS	480	234	246	

TEST STATISTICS			
	STATISTIC	D.F.	P-VALUE
GENERALIZED WILCOXON (BRESLOW)	18.065	1	0.0000
GENERALIZED SAVAGE (MANTEL-COX)	14.878	1	0.0001

DEAD = Number of patients who have responded, i.e. died in CCR of relapsed.

CENSORED = Number of patients withdrawn, i.e. the number of patients in CCR at close date.

Fig.2 is a graphical illustration of the cumulative proportions of females and males surviving in CCR as shown in Table 1.

By using grouping variables, in this case sex, and comparing the times to response for different values of the grouping variables, good information on prognostic factors such as sex, age and WBC is obtained. A further possibility is to make the analysis below for two or more grouping variables, e.g. duration of remission for different risk groups of female and male patients.

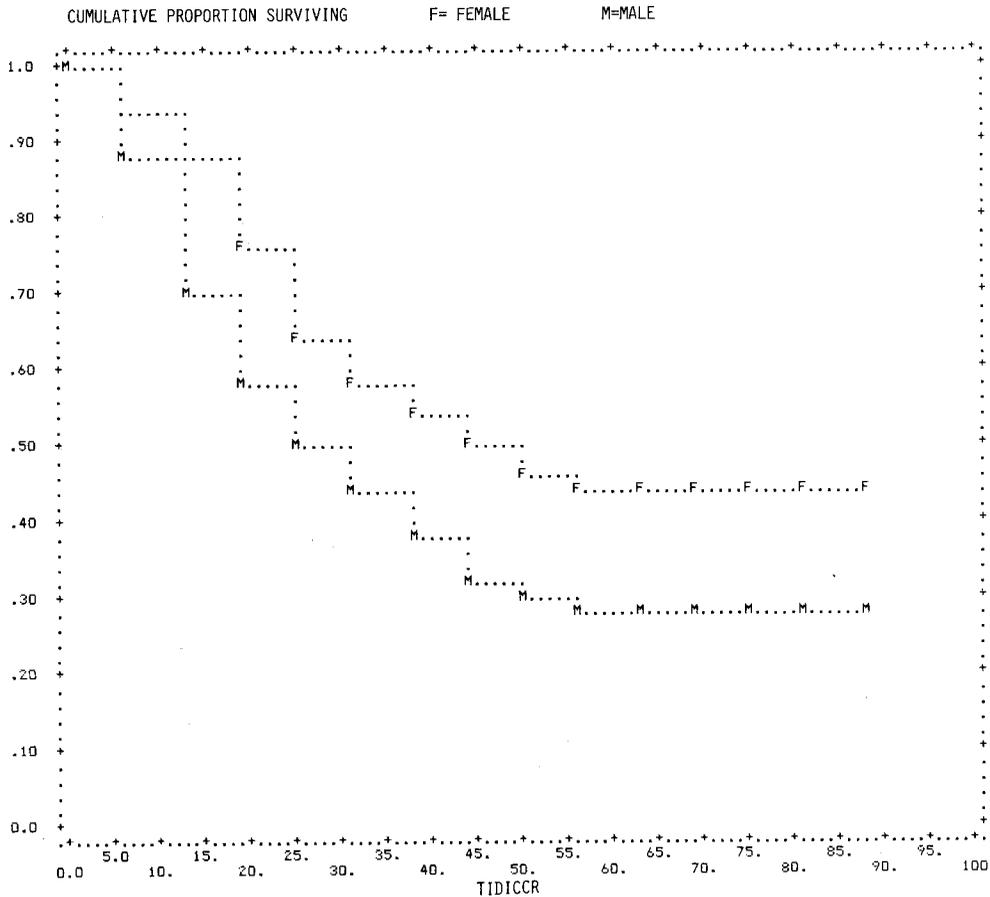


Fig.2 Plot of the cumulative proportions of females (F) and males (M) surviving in CCR versus time in CCR in months.

The PHGLM Procedure (2,4)

The Cox proportional hazard linear model to one dependent variable can determine the "best" variable to be added to a model in a model explaining time in CCR (TCCR), i.e. the variation in TCCR will be explained by a set of explanatory variables. But as these variables sometimes explain the same variation (are correlated with each other), the strength of the different variables explaining TCCR will be obtained, provided that the other variables are in the model.

Table 3 is the computer print out taken from the last step in the PHGLM Procedure, SAS SUPPLEMENTAL LIBRARY USER'S GUIDE, 1980 (4). In the print out BETA is comparable with parameters in a multiple linear regression model. CHI-SQUARE is a measure of the

strength of the variable and the P value is the level of significance for the variable in the model. The D value gives a measure of the contribution of the variables explaining the variation in TCCR.

The solution gives an answer to the question which variables are the most important of those affecting duration in CCR and is also a measure of the strength of these variables.

Table 3. Summary of the PHGLM Procedure (computer print out).

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SURVIVAL IN ALL 3
16:10 TUESDAY, DECEMBER 1, 1981

STEPWISE PROPORTIONAL HAZARDS GENERAL LINEAR MODEL PROCEDURE

DEPENDENT VARIABLE: TIDICCR SURVIVAL TIME
EVENT INDICATOR: LIC

VARIABLE      BETA      STD. ERROR    CHI-SQUARE    P      D
LPK           0.00266249  0.00041516    41.13         0.0000 0.124
KON           0.31054665  0.13139369    5.59          0.0181 0.019
ALDER        0.00365191  0.00169567    4.64          0.0313 0.016
MEDT         0.17321388  0.08517534    4.14          0.0420 0.014

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CHI-SQUARE Q STATISTICS ADJUSTED ONLY FOR VARIABLES IN THE MODEL

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VARIABLE    CHI-SQUARE    P      D
CNS         0.03         0.8714 0.000

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NO ADDITIONAL VARIABLES MET THE 0.1000 SIGNIFICANCE LEVEL FOR ENTRY.

Explanations to the Table:

LPK = WBC, KON = Sex, ALDER = Age, MEDT = Mediastinal tumor.

The variable CNS is not included in the model because it does not contribute enough to the explanation. The higher the D value of a variable, the stronger the influence of this variable on the duration of CCR.

COMMENTS

The aim of this communication is to demonstrate in a practical way how we have used standard computer programs in the evaluation of the influence of different clinical parameters on the outcome of a malignant disease.

The most important factor in this kind of analysis is the quality of the selected material. This must be as complete as possible and selection should be avoided. If there is selection, its conse-

quences must be analysed separately. Selection always implies a risk of irrelevant correlations, which can lead to wrong conclusions concerning the material. In our case there is no known selection, as the material includes all known cases of ALL in children in Sweden during the period in question. No child was lost at follow-up, which gives important strength to the material.

Frequency tables and cross tables analyse the material with regard to the distribution of different variables, e.g. age, sex, risk group, location of relapse, etc. The variables can be plotted against each other in a desired way. For instance the relation between duration of CCR and age or sex can easily be determined, but the tables are difficult to read and the results are not easy to evaluate.

Life table analyses (1) offer better possibilities than frequency tables and cross tables of studying variables affecting the duration of CCR versus clinical parameters and different treatment programs. The life table method gives a graphical illustration of time in CCR against parameters such as age, WBC, treatment programs and so on. It also permits mutual comparisons of subgroups in the material, e.g. "standard risk patients" against "high risk patients" with regard to sex or age. These analyses will yield variables explicitly describing the duration of CCR. The problem is that in one individual patient, different parameters often interact with regard to the outcome of the disease. It may thus be difficult to estimate the effect of a single parameter. We have used a linear regression analysis as described by Cox (2) to solve this problem. This method implies a listing of the internal order of the variables with regard to their influence on the outcome of the disease (Table 3).

Thus we have evaluated the strength of various "high risk criteria" in childhood lymphoblastic leukemia.

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