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Sex and other prognostic factors in acute lymphoblastic leukemia in childhood

ABSTRACT

A complete national material of children with acute lymphoblastic leukemia diagnosed in the years 1973–1980 was analyzed with regard to prognostic differences between males and females. In accordance with international criteria (age, WBC, CNS involvement, and mediastinal mass), the children were classified as standard risk (SR) and increased risk (IR). Thirty-eight percent of the males and 32% of the females fulfilled criteria for assignment to the group with an increased risk.

A linear multiple regression analysis on the material showed that WBC was the most important prognostic criterion, followed by sex, age, and mediastinal mass. The prognosis was significantly poorer for males in the standard risk ($p < 0.03$) and in the increased risk group ($p < 0.0001$). The IR criteria were more valid for males than for females. Serious complications resulting from therapy were more frequently reported for females than for males. These studies suggest that sex is of significance both for the prognosis and for the efficacy of treatment.

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In children with acute lymphoblastic leukemia (ALL), the outcome of the disease will be influenced by certain characteristics at diagnosis, such as the initial white blood cell count (WBC), age, the presence or absence of a mediastinal mass and of CNS involvement, and the type of leukemia according to immunological typing of the malignant cells.[1] Prognostic differences between the sexes, favoring females, have been observed in some materials, and these have been more frequently evident after discontinuation of therapy.[1–5] Other authors have found no such sex differences.[6–8]

The aim of this investigation was to study this question further and to analyze the criteria for classification as "increased risk" among males and females separately. The study was performed on a complete national material of children with ALL. There was no treatment selection with regard to sex.[9,10]

PATIENTS AND METHODS

In the years 1973–1980, 508 children in Sweden (< 16 years of age) were diagnosed as having ALL. Treatment in accordance with the programs of the Swedish Child Leukemia Group was given to 487 of these children. The same treatment was given to males and females. In 21 children the treatment received was incomplete, without adequate CNS prophylaxis. The treatment programs implied progressively more intensified cytostatic therapy over the years.[9] From 1976, the children were classified into risk categories, namely standard risk (SR) and increased risk (IR). The criteria for IR patients were: an age at diagnosis of

TABLE 1.

Clinical Findings at Diagnosis of ALL in 233 Females and 275 Males Diagnosed between 1973-1980

	Percent of 233 Females	Percent of 275 Males
Age <1 year	1	2
1-2 years	8	4
2-10 years	78	74
10-12 years	7	11
>13	6	9
	100	100
Mediastinal mass	6	13
CNS involvement	2	5
WBC $\times 10^9$/l		
<20	67	67
20-50	18	12
50-100	7	9
>100	8	12
	100	100
Standard risk	68	62
Increased risk	32	38
	100	100

<1 year or >13 years, CNS involvement, the presence of a mediastinal mass, and WBC at diagnosis of $>50 \times 10^9$/l (since 1978 $>20 \times 10^9$/l). Classification by cell-surface markers did not start until 1978, and therefore evaluation with regard to this criterion was not possible.

Information concerning the children was obtained from all 45 Departments of Pediatrics in Sweden by an inventory carried out in January 1982, thus giving an observation time of 1–9 years. For statistical analysis of the material, standard life tables and survival functions[11] were used and linear regression analysis[12] was performed.

TABLE 2.

Results of Linear Regression Analysis of 508 Children with ALL Diagnosed between 1973-1980 with Regard to Sex and Criteria for Increased Risk

Variable	Chi-square	Probability
WBC	42	<0.001
Sex	6	0.02
Age	4.5	0.03
Mediastinal mass	4.1	0.04
CNS involvement	0.3	0.9

RESULTS

The proportions of males and females in different age groups are given in Table 1, which also shows the distribution with regard to clinical findings at diagnosis. All criteria for IR were more frequently fulfilled among males than among females; thus 38% of the males and 32% of the females were IR patients. Table 2 gives the result of the PHGLM procedure,[12] a method of linear regression analysis which estimates the influence of various variables (WBC, age, CNS involvement, presence of mediastinal mass, and sex) on the duration of continuous complete remission (CCR). WBC appeared to be the most important prognostic

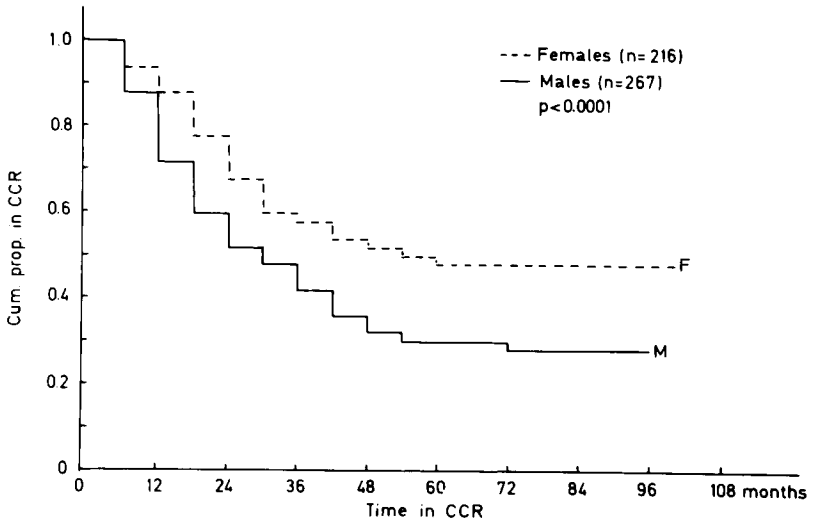

FIGURE 1
Cumulative proportions surviving in CCR among males (M) and females (F) with achieved remission ($p < 0.0001$).

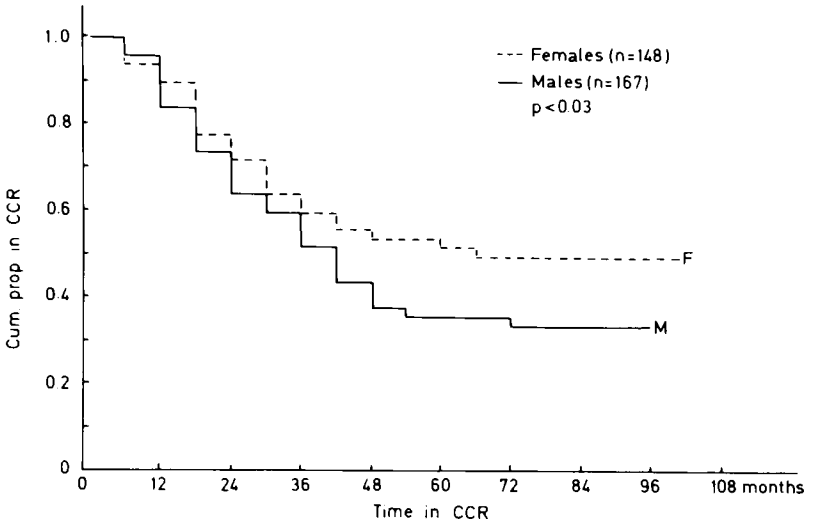

FIGURE 2
Cumulative proportions surviving in CCR among SR males (M) and SR females (F) with achieved remission ($p < 0.03$).

factor, followed by sex, age, mediastinal mass, and—least important with no significance—CNS involvement.

Figure 1 shows the cumulative proportions of males and females surviving in CCR among all children who achieved remission (483/508 children). This proportion was significantly higher for females than for males ($p < 0.0001$). The difference was less significant in the SR group (Fig. 2, $p < 0.03$) than in the IR group (Fig. 3, $p < 0.0001$). These sex differences persisted even when the males with testicular relapses were excluded from the material.

Figures 4 and 5 give the corresponding proportions of males and females in CCR in various age groups. Among the females there were no significant differences in survival in the age groups between 1 and 13 years. Among the males, an age of <2 years or >10 years at diagnosis implied a poorer prognosis than an age of 2–10 years at diagnosis.

The differences in survival with regard to WBC

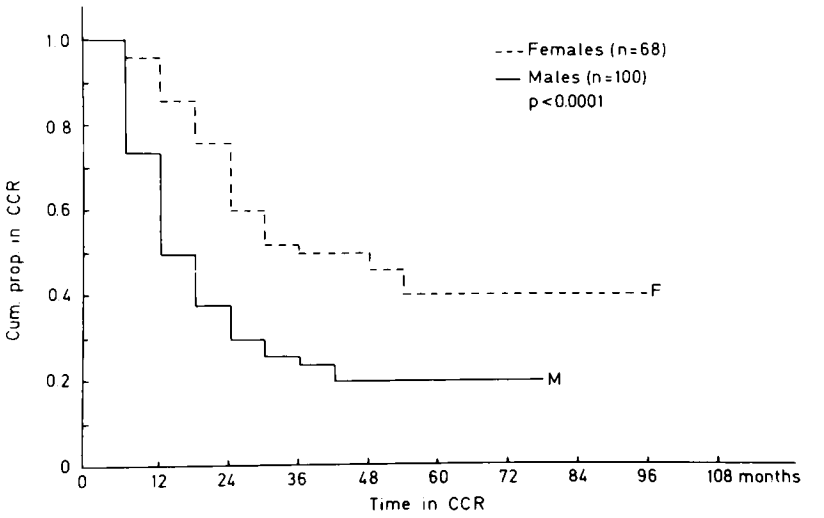

FIGURE 3
Cumulative proportions surviving in CCR among IR males (M) and IR females (F) with achieved remission ($p < 0.0001$).

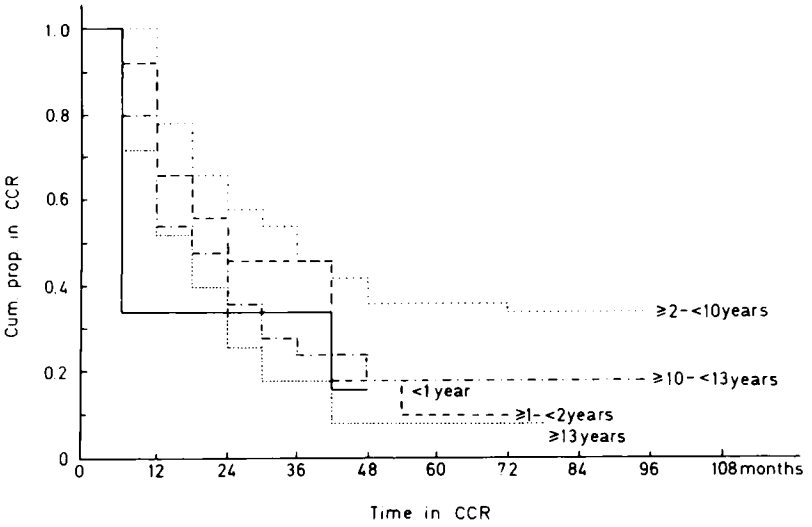

FIGURE 4
Cumulative proportion of males with achieved remission surviving in CCR, with regard to age at diagnosis (n = 267).

count at diagnosis are illustrated in Figures 6 and 7. There were differences between males and females in all groups, but the difference was most pronounced for a WBC count of 50–100 × 10⁹/l ($p < 0.0001$).

Figure 8 shows the proportions of males and females in CCR after termination of therapy. The difference between the sexes was significant ($p < 0.02$). This difference was completely abolished, however, when the males with testicular relapses were excluded from the material.

Figure 9 illustrates the probability density function for males and females in the whole material, i.e., the probability of relapse or death during CCR from the time of achieved remission. Males show an earlier and higher peak than females and there is also a small peak for males after discontinuation of therapy.

The reported serious side effects of therapy are summarized in Table 3. There was a significantly higher proportion ($p < 0.05$ of afflicted females than of afflicted males in the induction period

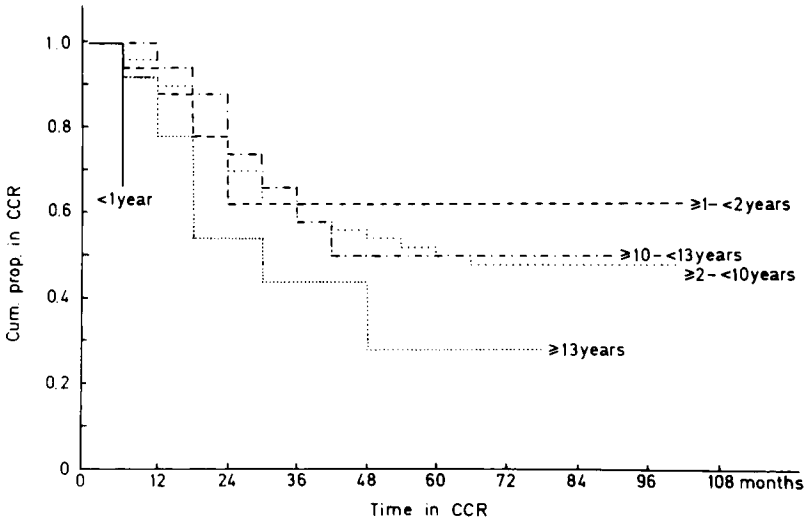

FIGURE 5
Cumulative proportion of females with achieved remission surviving in CCR, with regard to age at diagnosis (n = 216).

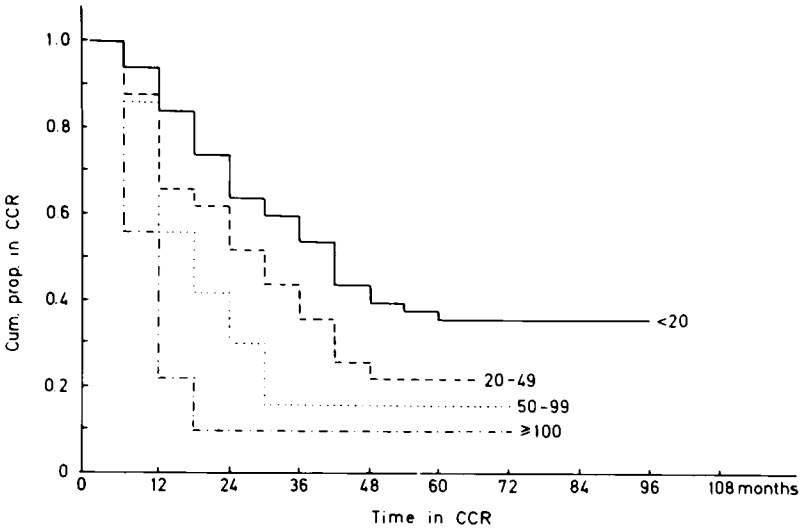

FIGURE 6
Cumulative proportions of males with achieved remission surviving in CCR, with regard to WBC counts ($\times 10^9/l$) at diagnosis (n = 267).

(fatal outcome, septicemia, and severe bleeding). In the consolidation phase (complications of CNS treatment) and the maintenance period (fatal outcome, severe infections, and bleeding), there were more afflicted females than males, though the differences were not statistically significant.

DISCUSSION

A number of reports have pointed to the male sex as a negative prognostic factor in childhood ALL.[2 5] Other authors, however, have found no significant difference with regard to sex.[6–8] The findings in one large investigation[5] indicate that with a more intensified cytostatic regime, and especially with adequate CNS prophylaxis, the sex differences in the prognosis will be more pronounced.

We have analyzed a national, uniform, and unselected material comprising all known children with ALL diagnosed in Sweden from 1973–80 with regard to various clinical criteria and with

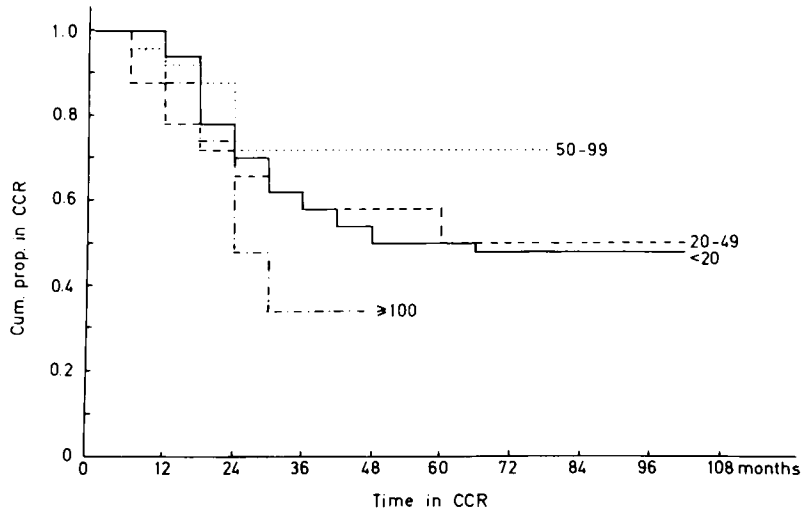

FIGURE 7
Cumulative proportion of females with achieved remission surviving in CCR, with regard to WBC counts ($\times 10^9/l$) at diagnosis (n = 216).

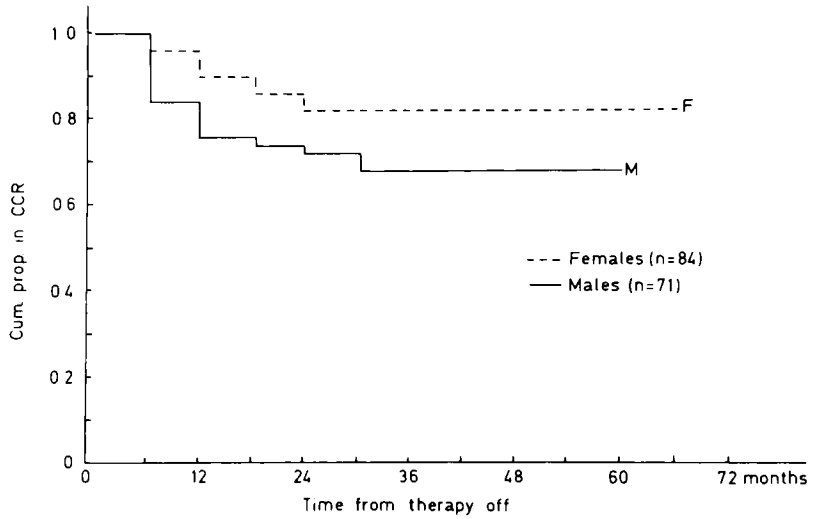

FIGURE 8
Cumulative proportions surviving in CCR among males (M) and females (F) with discontinued therapy ($p < 0.02$).

special emphasis on sex as a prognostic factor. In spite of the change in therapy during this period, males and females are quite comparable, as they received the same therapy in all treatment programs used. We found sex to be the second most important prognostic factor, with a pronounced difference between males and females not reported earlier.

ALL is not one disease entity but a group of diseases, as reflected by the various clinical findings in the patients at diagnosis. These variations in clinical parameters are also correlated to the prognosis and have become a reason for classifying leukemia patients into SR and IR groups. In the present material, we found that the criteria for IR were more commonly fulfilled among males than among females (38% and 32% of the groups). This, however, only partly explains the differences in prognosis between males and females. We found that the prognosis was better for females than for males in both the SR (Fig. 2) and the IR group (Fig. 3), but the difference was more pronounced

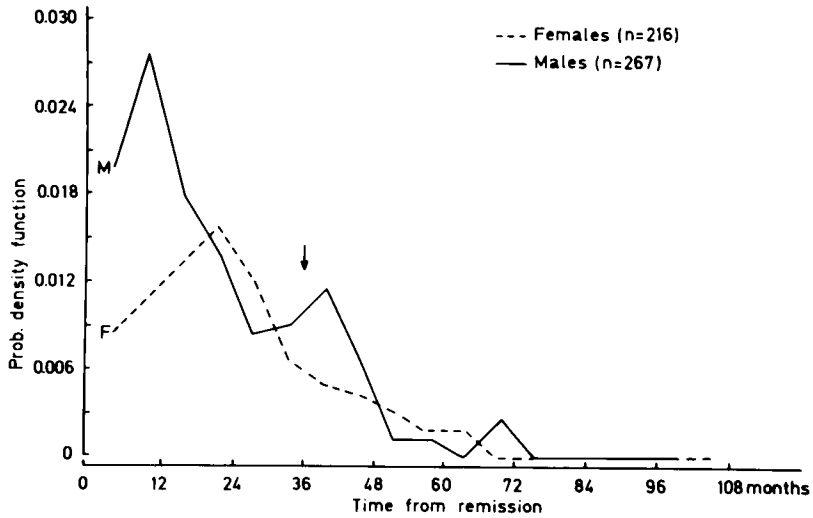

FIGURE 9
Probability density function (see text) for males (M) and females (F) surviving in CCR. Arrow indicates time of discontinuation of therapy.

TABLE 3.
Mortality and Severe Complications ascribed to Therapy in 233 Females and 275 Males with ALL Diagnosed between 1973-1980

Treatment Period	Females (n = 233)		Males (n = 275)	
	Number	Percent	Number	Percent
Induction				
Mortality	17	7	8	3
Severe complications	52	22	47	17
	69	29	55	20
Consolidation				
Severe complications	52	22	49	18
Maintenance				
Mortality	13	6	9	3
Severe complications	40	17	45	16
	53	23	59	19

in the latter group. Testicular relapses have partly explained the difference in some materials.[3,5] This was also true in the present material concerning prognosis after discontinuation of therapy, since no sex difference was found when testicular relapses were excluded. During therapy, however, the proportion of males in CCR was significantly lower than that of females even when testicular relapses were excluded. This shows that the poorer prognosis for males must be explained by other factors than testicular relapses. In an analysis of the WBC count at diagnosis, we found significant sex differences in all WBC values, favoring females; these were most pronounced in the WBC group 50–100 $\times$ $10^9/1$, with a p value of <0.001.

After classification of the patients into different age groups (Figs. 4 and 5), we noted marked prognostic differences in the males between the age groups of 2 and 10 years on the one hand, and the groups below 2 years and above 10 years, on the other. In the females there were no significant differences in the age groups between 1 and 13 years of age, which is remarkable and not reported earlier to our knowledge. The IR criteria used in this material thus proved to be more valid for males than for females, with regard to length of time in CCR and thus, probably, also for the overall prognosis.

Sexual differences with regard to prognosis have been described earlier, but no explanations are known. Baumer[4] suggests that there may be a subtype of ALL, not yet completely identified, which is more common in males and has a poorer prognosis, which might explain the sex differences in incidence and prognosis. Sather et al.[5] found that the introduction of extensive CNS prophylaxis provided greater benefit to females. They propose that differences in the proportion of cell-surface markers between males and females could explain some of the sexual differences in prognosis. This may be true, although we have not been able to confirm this in the present material. On the other hand, Chessels' study[13] showed a good correlation between high WBC count, mediastinal mass, and the presence of T-cell leukemia, which is the immunologically identified subtype of ALL with the worst prognosis. Consequently, most but not all of the patients with T-cell leukemia will be IR patients according to clinical parameters.

One possible reason for the findings may be differences between males and females concerning therapeutic effectiveness. We found that complications of therapy were more often reported in females than in males (Table 3). Therefore, we suggest that females are more susceptible to treatment than males and consequently that males perhaps need higher doses of cytostatics to get the same chance of cure. Further studies on concentrations of cytostatics in various body compartments during treatment remain to be performed. Few such studies have been undertaken hitherto, and no valid data on cytostatic concentrations are available, especially with regard to sex differences. □

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