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Malnutrition as a prognostic factor in lymphoblastic leukaemia: a multivariate analysis

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Abstract

One hundred and twenty eight Brazilian children with lymphoblastic leukaemia were intensively treated with a Berlin-Frankfurt-Munich based protocol. More children had a white cell count above 50×10^9/l (31%) then observed in developed countries. After a median follow up of 31 months (11–58 months), the estimated probability of relapse free survival was 41% (7%) for the whole group. After adjustment in the Cox's multivariate model, malnutrition was the most significant adverse factor affecting duration of complete remission. Age above 8 years and high peripheral white cell count were also significant adverse factors. Among the nutritional indices, the height for age and weight for age z scores were both significant, whether the cut off points of $z=-2$ or $z=-1{\cdot}28$ were chosen to define malnutrition. A strong statistical association between the two indices was found; the contribution of height for age z score to the prediction of relapse free survival was more significant. Children with height for age z score <-2 had a relapse risk of 8·2 (95% confidence interval 3·1 to 21·9) relative to children with z score >-2. The results of this study suggest that socioeconomic and nutritional factors should be considered in the prognostic evaluation of children with leukaemia in developing countries.

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The event free survival of children with acute lymphoblastic leukaemia (ALL) in developed countries has increased substantially in the last two decades. Treatment with intensive protocols has brought the estimated probability of event free survival at 6–7 years close to 75%.[1–3] Although the prognosis of ALL has also improved in underdeveloped countries, the figures for event free survival are lower, even when aggressive protocols are used.[4]

Unfavourable socioeconomic factors could contribute to this observation and there is some previous evidence for their important role. Australian children from the upper social classes had a significantly better five year survival rate and duration of first remission than children from the lower social classes.[5] Asian (Indian and Pakistani) children living in the UK showed a poorer prognosis than native white children.[6] In Baltimore, among 23 white children of low socioeconomic status the two year survival rate was 28% and that of 22 children of high socioeconomic status was 51% ($p<0{\cdot}005$).[7] The End Results Group in the US reported a significant difference between the one year survival rate of 1541 white children treated at private hospitals compared with 134 white children treated at county and charity hospitals.[8]

Mexican investigators demonstrated, for the first time, that malnutrition was an adverse prognostic factor in the outcome of children with standard risk ALL.[9] Among 43 such patients, the five year disease free survival was 83% for well nourished children and 26% for undernourished children ($p<0{\cdot}001$). The main reason for the observed difference was the significantly higher rate of bone marrow relapse in the latter.

In this prospective study, we analysed the outcome of 128 children treated with an intensive protocol to determine the influence of nutritional status on the probability of overall survival and duration of first complete remission. The concomitant effect of other well known predictive variables was accounted for by a multivariate analysis.

Patients and methods

PATIENT ELIGIBILITY

Eligible for inclusion in the study were previously untreated children under 15 years of age with the diagnosis of ALL. The diagnosis was made on the initial bone marrow smear stained by May-Grünwald-Giemsa (MGG) and confirmed by appropriate cytochemical stains (Sudan black, periodic acid Schiff (PAS), and dual esterase). Exclusion criteria were FAB classification type L3 leukaemia, second tumour leukaemia, presence of previous chromosomal disease, and parental refusal to participate in the study. Two children were excluded because the diagnosis of ALL on MGG smears was not confirmed cytochemically.

PATIENT POPULATION

From January 1988 to December 1991, 128 children were included in the study. They were diagnosed in five health institutions of Belo Horizonte, Brazil, organised within a cooperative group for the treatment of acute leukaemia in the state of Minas Gerais (GCMTLA). Two

Table 1 Patient characteristics at diagnosis of ALL (n=128)

Sex (M:F)	68:60
Median (range) age in months	70 (9–177)
Median (range) white cell count ($\times 10^9$/l)	14·9 (0·4–620)
Mean (range) weight for age z score*	−0·56 (−3·66 to +3·67)
Mean (range) height for age z score*	−0·435 (−4·05 to +2·98)
Mean (range) weight for height z score*	−0·34 (−3·31 to +3·56)
FAB morphology (L1:L2)†	88:36
Cytoplasmic vacuolation (negative:positive)‡	89:35
Reaction to PAS (negative:positive)§	81:30

*z Score=SD score.
†FAB morphology according to the criteria from the Children's Cancer Study Group.[10] Less than 25% of blasts with L2 morphology=L1 leukaemia; otherwise, L2 leukaemia.
‡Less than 10% of vacuolated blasts=negative; otherwise, positive.
§Less than 5% of PAS positive blasts=negative; otherwise, positive.

institutions were responsible for the treatment of 105 children (82%). The number of patients admitted to the study was evenly distributed over the four years. Among the 128 cases, seven children abandoned treatment (five during the induction phase and two during consolidation). The minimum follow up for patients alive at the date of analysis (1 November 1992) was 319 days and the maximum 1740 days (median 941 days). Patient characteristics are summarised in table 1. The proportion of children presenting with a total white cell count over 100×10^9/l at diagnosis was 15% and over 50×10^9/l was 31%. There were only two children younger than 12 months at diagnosis; 16 (12·5%) were 10 years or older. Immunophenotyping was available for only a limited number of children and will not be presented. Cytogenetics has become available only recently for children included in the protocols of GCMTLA.

PATIENT TREATMENT

The protocols were approved by the appropriate institutional review boards and informed consent was obtained for all patients.

Table 2 Consolidation regimens for standard and very high risk groups

Treatment	*Dose and route*	*Days treatment given*
Standard risk group		
Triple IT therapy*	Intrathecal	1, 15, 29, 43, 70, 77
Methotrexate with folinic acid rescue	500 mg/m²/dose (1/10 push, 9/10 continuous intravenous 24 hours); 12 mg/m²/dose 48 and 54 hours after starting methotrexate	1, 15, 29, 43
6-Mercaptopurine	25 mg/m²/day (by mouth)	1–56
Vincristine	1·5 mg/m²/day (intravenous)	57, 64
Doxorubicin	25 mg/m²/day (intravenous)	57, 64
L-asparaginase	10 000 U/m²/dose	57, 60, 64, 67
Dexamethasone	10 mg/m²/day (by mouth)	57–70, then taper
Cytarabine	75 mg/m²/day (intravenous)	70–73, 77–80
Thioguanine	50 mg/m²/day (by mouth)	70–84
Very high risk patients		
Triple IT therapy*	Intrathecal	1, 15 29, 43, 106, 113
Methotrexate with folinic acid rescue	500 mg/m²/day (1/10 push, 9/10 continuous intravenous 24 hours); 12 mg/m²/dose 48 and 54 hours after starting methotrexate	1, 15, 29, 43
Prednisone	100 mg/m²/day (by mouth)	1–5, 15–19, 29–33, 43–47
Cytarabine	300 mg/m²/dose (intravenous)	6–7, 20–21, 34–35, 48–4
Teniposide	150 mg/m²/dose (intravenous)	6–7, 20–21, 34–35, 48–49
Mitozantrone	10 mg/m²/dose (intravenous)	6, 20, 34, 48
Dexamethasone	10 mg/m²/day (by mouth)	71–92, then taper
Vincristine	1·5 mg/m²/day (intravenous)	78, 85, 92, 99
Doxorubicin	25 mg/m²/day (intravenous)	78, 85, 92, 99
Cyclophosphamide	1 g/m²/dose (intravenous)	106
Cytarabine	75 mg/m²/day (intravenous)	106–109, 113–116
Thioguanine	50 mg/m²/day (by mouth)	106–119
Cranial radiotherapy	12 Gy (1–2 years), 18 Gy (>2 years)	106–119

*Triple intrathecal (IT) therapy: methotrexate, 6 mg for children <1 year, 8 m for 1—2 years, 10 mg for 2–3 years, and 12 mg for children >3 years; cytarabine: 30 mg/m², maximum 50 mg; dexamethasone: 2 mg/m², maximum 2 mg.

The treatment was based on the German Berlin-Frankfurt-Munich (BFM)-83 protocol for childhood non-B ALL.[11] All children received the same eight week induction regimen (BFM protocol I): prednisone, vincristine, daunorubicin and L-asparaginase, followed by cyclophosphamide, cytarabine, and 6-mercaptopurine. They were then assigned to four alternative consolidation regimens according to three criteria. (1) Those who had not achieved a complete remission after the first phase of the induction regimen (before cyclophosphamide administration) were all assigned to the very high risk group. (2) Early remitted patients were categorised into the standard or high risk groups depending on the BFM risk factor, calculated from the initial peripheral blast cell count and the size of the spleen and liver.[11] Children with the BFM risk factor at or below 0·8 were assigned to the standard risk group. (3) Children in the high risk group (risk factor over 0·8) were randomised to receive either protocol 1 (intermediate dose methotrexate and triple intrathecal chemotherapy for a year as central nervous system prophylactic treatment) or protocol 2 (cranial radiation plus limited triple intrathecal treatment). The consolidation regimens are summarised in tables 2 and 3. All children received maintenance chemotherapy which included oral 6-mercaptopurine (reference dosage 50 mg/m²/day) and oral methotrexate (20 mg/m²/week). The 6-mercaptopurine dosage was adjusted to keep the white cell count between 2 and 4×10^9/l. The total duration of treatment for all children was two years. There were two exceptions to these guidelines: children in the high risk group and less than 12 months old at diagnosis were automatically assigned to the high risk group regimen 1 and children with initial central nervous system involvement received weekly triple intrathecal treatment until disappearance of blasts from the cerebrospinal fluid, then monthly for a year followed by radiotherapy (2400 cGy to the cranium and 1200 cGy to the spine). They were assigned to the high risk group 2 consolidation regimen or to the very high group depending on bone marrow remission status after phase I of the induction regimen.

Although all children should have received L-asparaginase as part of the induction regimen, this particular drug was not available for the whole duration of the study: 59 children were given L-asparaginase according to protocol; 69 were not (six did not survive to the scheduled L-asparaginase day and five did not complete the eight dose L-asparaginase course).

LYMPHOBLAST MORPHOLOGY

The FAB classification, modified by Miller,[10] was used by two independent cytologists to categorise the diagnostic bone marrow smear. When the proportion of L2 blasts was below 25% (mean of two observers) the leukaemia was classified as L1. The PAS reaction in the marrow lymphoblasts was considered negative

Table 3 Consolidation regimens for high risk group according to randomisation

Treatment	Dose	Days treatment given
High risk patients (randomised group 1)		
Triple IT therapy*	Intrathecal	1, 15, 50, 64
Methotrexate with folinic acid rescue	500 mg/m^2/dose (1/10 push, 9/10 continuous intravenous 24 hours); 12 mg/m^2/dose 48 and 54 hours after starting methotrexate	1, 15, 50, 64
6-Mercaptopurine	25 mg/m^2/day (by mouth)	1–28, 50–78
Cytarabine	300 mg/m^2/dose (intravenous)	29–30, 36–37
Teniposide	150 mg/m^2/dose (intravenous)	29–30, 36–37
High risk patients (randomised group 2)		
Dexamethasone	10 mg/m^2/day (by mouth)	1–22, then taper
Vincristine	1·5 mg/m^2/day (intravenous)	1, 8, 15
Doxorubicin	25 mg/m^2/day (intravenous)	1, 8, 15
Cytarabine	300 mg/m^2/dose (intravenous)	22–23, 29–30
Teniposide	150 mg/m^2/dose (intravenous)	22–23, 29–30
6-Mercaptopurine	25 mg/m^2/day (by mouth)	43–57
Triple IT therapy*	Intrathecal	43, 50, 57
Cranial radiotherapy		43–57

*Triple intrathecal (IT) therapy: methotrexate, 6 mg for children <1 year, 8 m for 1—2 years, 10 mg for 2–3 years, and 12 mg for children >3 years; cytarabine: 30 mg/m^2, maximum 50 mg; dexamethasone: 2 mg/m^2, maximum 2 mg.

when less than 5% (mean of three observers) of blasts gave a positive granular or block-type reaction to PAS. Cytoplasmic vacuolation was considered negative when less than 10% (mean of two observers) of vacuolated blasts were present. Remission was defined as fewer than 5% blasts in the marrow and no evidence of extramedullary leukaemia. Relapse was defined as greater than 25% blasts in the bone marrow or evidence of extramedullary leukaemia.

ASSESSMENT OF NUTRITIONAL STATUS

All children had their height and weight measured at diagnosis. One child who had his weight registered only after 15 days of prednisone treatment was excluded from weight analysis. Three nutritional indices were evaluated: weight for age, height for age, and weight for height. They were expressed as SD scores (z score) in relation to the National Center for Health Statistics population.[12] Standardised prevalence of malnutrition was defined as the proportion of cases in the observed population outside the normal distribution of the reference values, according to Mora.[13] For the individual child, the cut off point to discriminate between 'undernourished' and 'well nourished' was $z=-2$ (World Health Organisation (WHO) working group recommendation[14]). A more sensitive although less specific cut off point of $z=-1{\cdot}28$ (10th centile) was also chosen to analyse the data.[15]

STATISTICAL METHODS

The association of the nutritional variables was assessed by the Fisher's exact test. The association of two continuous variables was evaluated by Spearman's correlation coefficient.

For analysis of event free survival, events were defined as relapses, remission deaths, second tumours, or absence of remission (event free survival=0); failure times were calculated from the day of diagnosis. For analysis of the continuous remission failure times were calculated from the day of remission and events were defined as relapses, remission death, or second tumours. All death regardless of cause were counted for the analysis of overall survival and survival times were calculated from the day of diagnosis. Seven children who abandoned treatment were evaluated on the day of the last visit. Data were analysed as of 1 November 1992.

The Kaplan-Meier method was used to estimate event free survival, continuous complete remission, and overall survival functions.[16 17] Differences between patient subgroups were assessed by the two sided log rank test.

Cox's regression model was used to estimate the hazard ratios of recurrence due to the combined effects of two or more prognostic factors.[18 19] Inference was based on the partial likelihood functions.[20] All models were fitted after stratification of cases by the hospital of treatment. The final model containing the most parsimonious subsets of study factors with independent predictive properties with respect to the risks of recurrence was achieved by a stepdown procedure. Because of the known prognostic importance of age and white cell count at diagnosis, these variables were not excluded from the model until there remained a variable with a p value $>0{\cdot}15$ to be eliminated, even if its p value was lower than those from age and white cell count. Computational work was done with EGRET (1988) software.

The variable PAS (reactivity of lymphoblasts to PAS) could not be included in the Cox's model due to violation of the proportionality assumption that underlies the method. Its influence on the risk of relapse was investigated by the stratified log rank test,[21] which compared PAS positive against PAS negative cases stratified by the significant variables provided by the Cox's final model.

Results

NUTRITIONAL STATUS

Figure 1 depicts the distribution curves of weight for age and height for age in relation to the reference z scores. Standardised prevalence of malnutrition was 21·2% when the indicator weight for age was chosen and it was 17·4% when the height for age indicator was considered. Height for age and weight for age were strongly associated. Whereas only two out of 114 children with height for age z score above -2 had a weight for age z score below -2, six out of 13 children with height for age z score below -2 had the weight for age z score below -2 ($p=8\times10^{-6}$). Weight for age and weight for height were also associated variables ($p=0{\cdot}0013$).

OVERALL SURVIVAL AND DURATION OF COMPLETE REMISSION

Table 4 summarises the clinical course of the patient population. The remission rate was 94% (120/128 patients). The estimated probability (SE) 58 month overall survival was 62% (5%), the 58 month event free survival 40% (6%), and the 57 month continuous

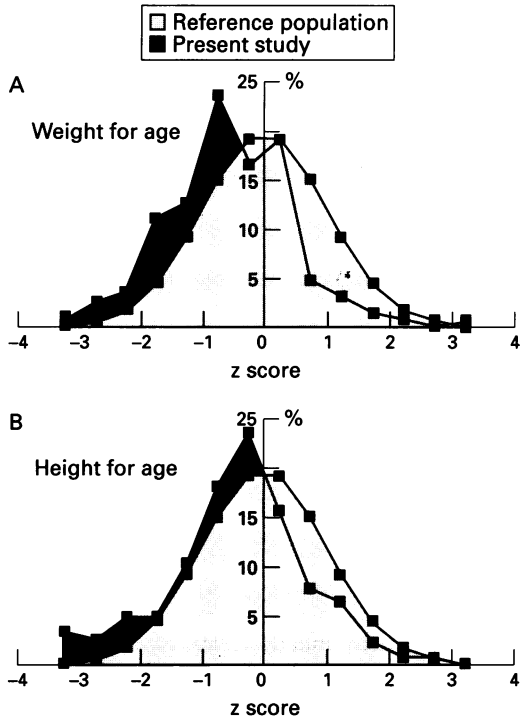

Figure 1 Standardised prevalence of malnutrition considering the weight for age (A) or height for age (B) z score as the nutritional indicator in the patient population. The lightly shaded areas correspond to the normal distribution of the reference population.[12] The heavily shaded areas represent the excess of children in the lower z scores. Calculated by the method proposed by Mora,[13] the standardised prevalence of malnutrition was 21·2% (A) and 17·4% (B).

complete remission 41% (7%). Of 41 recorded relapses, 27 took place during treatment and 14 off treatment (of these, two were second tumour relapse, namely acute granulocytic leukaemia). Isolated bone marrow relapse occurred in 25 children, isolated central nervous system relapse in four, isolated testicular relapse in eight, and combined relapse in three children; one child had an ocular relapse.

UNIVARIATE ANALYSIS OF PROGNOSTIC FACTORS

The influence of malnutrition on the duration of continuous complete remission is illustrated in fig 2. While the estimated five year probability of continuous complete remission for children with height for age z score above −2 was 45% (7%), no undernourished child has completed 2·5 years continuous complete remission (p=0·00001). The same estimates for the cut off point of z=−1·28 were respectively 45% (8%) and 16% (10%), p=0·00004.

Of 10 children who achieved initial remission and had a height for age z score below −2, seven relapsed. This contrasts with 34 out of 103 children with the z score above −2. Of seven children who died in complete remission (three with sepsis, two with idiopathic interstitial pneumonia, one with pulmonary fibrosis, and one of unknown aetiology) only one had a height for age z score below −2.

Other unfavourable prognostic variables were: weight for age z score <−2 (p=0·0005), white cell count at diagnosis >75×10⁹/l (p=0·003), PAS negative reaction (p=0·025), age above 8 years (p=0·034), BFM risk factor >1·7 (p=0·05), and remission failure after phase I induction (p=0·06). Sex (p=0·34), weight for height (p=0·84), FAB morphology (p=0·098), cytoplasmic vacuolation (p=0·79), and L-asparaginase in the induction regimen (p=0·37) were not significant factors. The continuous complete remission Kaplan-Meier curves for the standard and high risk group (both with and without cranial radiation) were not significantly different. The estimated probability of five year continuous complete remission for the very high risk group (n=9) was 24% (20%) and that for the other three joined groups (n=102) was 43% (7%), p=0·032.

Table 4 Clinical course of 128 children with ALL

No of children in study			128
Death during induction of remission	5		
Therapy resistance	1		
Withdrawals from treatment	2		
No of remitters			120
Withdrawals from treatment	5		
Lost to follow up	0		
Relapses	27		
Death in remission	7		
In remission, still on treatment	27		
Partial total		66	
No of children off treatment			54*
Relapses		14†	
Alive in second line protocol	10		
Death	3		
Off treatment for second time	1		
Continuous complete first remission		40	

*One additional child had isolated central nervous system relapse and is off treatment after two years of treatment, in complete remission as of 1 November 1992.
†Two children suffered second tumour relapse (acute granulocytic leukaemia).

MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS

The final model stratified by the hospital of treatment contained five variables: age (p=0·041), initial white cell count (p=0·11), BFM risk factor (p=0·025), height for age z score (p=0·076), and weight for age z score (p=0·086). Due to the strong association between these two scores (see above and working group paper[14]), the latter was dropped from the model to show more clearly the effect of malnutrition on the risk of relapse. Similarly the white cell count and BFM risk factor were also highly associated (Spearman's correlation coefficient r=0·66, 95% confidence interval 0·55 to 0·75), and the white cell count was equally dropped to show more clearly the effect of the leukaemic mass on the risk of relapse. The final model is depicted in table 5.

When the analysis was repeated with the cut off point for the z scores at z=−1·28 (10th centile), no substantial change in the final model was observed (data not shown).

Positive PAS reaction in the lymphoblasts (>5% PAS positive marrow lymphoblasts) was a favourable prognostic factor in univariate analysis (p=0·025). However, after adjustment for age, initial white cell count and nutritional z scores (height and weight), PAS lost its statistical significance (stratified log rank test, p=0·16).

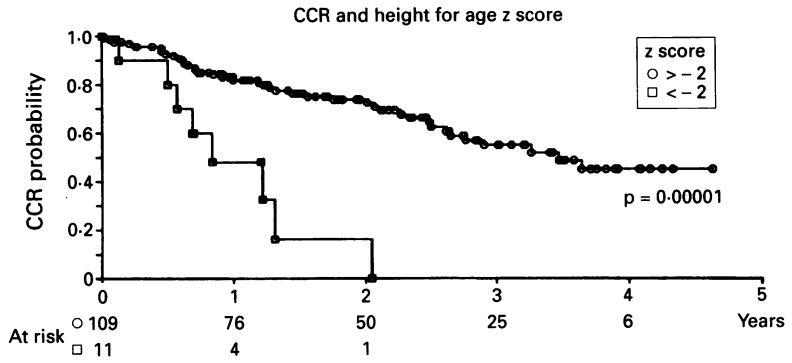

Figure 2 Kaplan-Meier plots for the duration of continuous complete remission (CCR) comparing children with the height for age z score below −2 and above −2, as of 1 November 1992. Each point on the curves represents one patient. The number of children at risk at the start of each time interval is shown at the bottom of the x axis. The log rank test yielded a p value=0·00001.

Discussion

The profile of the patient population differs in some fundamental aspects from that reported in developed countries. Although not excessive, the number of patients who abandoned treatment (7/128, 5·7%) is higher than the usual figure of less than 1 to 2%.[22] Economic problems and cultural barriers are associated with this event in developing countries. For instance, 10% of Saudi children[23] and 38% of Turkish patients[24] refused or did not complete the proposed treatment of ALL.

The age and sex distributions were similar to those reported elsewhere. The white cell count at diagnosis, however, was higher than usual. In our study 31% of children presented a white cell count over 50×10^9/l, the usual figure in developed countries being below 20%.[25] In Saudi Arabia 24 out of 80 children (30%) had a white cell count over 50×10^9/l.[23] As far as the BFM risk factor is concerned, 42·2% of patients had an index below 1·2 and 15·6% above 1·7. This is in sharp contrast with the respective 59·2% and 7·4% figures reported by the BFM-81 study.[1]

Another difference relates to the reactivity of the marrow lymphoblasts to the PAS reaction. Adopting the same cut off point for the definition of positive reaction (5%), 57% of British children,[26] and 64% of American children reported from the St Jude Hospital studies[27] were considered PAS positive. This contrasts with the finding of only 27% of PAS positivity in our population.

The prevalence of malnutrition in this study is, as expected, higher than in developed countries. The standardised prevalence of undernourishment was 21·2% when weight for age was chosen as the nutritional indicator and 17·4% when the height for age indicator was selected. These figures are conservative in relation to the actual prevalence of this phenomenon in the Brazilian population, because lower social classes frequently do not have proper medical care, which is essential for the diagnosis of ALL.

The remission induction rate of 94% is comparable with the results of other protocols. The frequency of deaths during this phase of treatment (4%) is somewhat higher than the figures reported in developed countries. The number of children dying in complete remission (5·8%) is higher than the figure of 2% reported by the BFM-81 study.[1] It is similar, however, to the UKALL VIII study frequency of 6·7%[28] and to the Latin American GLATHEM-84 study (7·7%[4]). The contribution of these factors to the observed lower estimated probabilities of event free survival and continuous complete remission as compared with other series from developed countries is,[1-3 28] therefore, relatively small.

A higher frequency of isolated or combined bone marrow relapse was the main reason for the interruption of complete remission in our study. Many relevant predictive risk factors for relapse were disclosed by the univariate analysis. In the multivariate model, however, only the white cell count (or the BFM risk factor), age, and malnutrition have retained statistical significant value (table 5).

The most important factor for relapse was malnutrition: the adjusted risk of relapse for undernourished children (height for age $z<-2$) was 8·2 greater (95% confidence interval 3·1 to 21·9) than that for well nourished children ($z>-2$). The same held true if the weight for age z score was chosen as the nutritional indicator. Weight for height z score was not a significant variable. It has been shown that weight for height and height for age together account for more than 95% of the variability in weight for age. This means that weight for age would represent the sum of the information given by the other two indices.[14] Height for age is, therefore, the relevant nutritional index which was able to predict leukaemic relapse in our study.

Deficits in height for age seem to reflect overall social conditions whereas weight for height is particularly important to describe current nutritional status. The first indicates a chronic stunting process and the latter a more acute wasting phenomenon.[14] It is conceivable, therefore, that socioeconomic factors might have played a relevant part in decreasing the estimated probability of relapse free survival in our patient population.

Because the prevalence of malnutrition is higher in Brazil compared with developed countries, the cut off point of $z=-1·28$ for the definition of nutritional status may be preferable to the less sensitive but more specific cut off point of $z=-2$, recommended by the WHO.[14] Whichever cut off point was chosen, height for age z score was the most powerful predictor of relapse.

Unfortunately other important biological prognostic factors were not available to us.

Table 5 Significant prognostic factors for the risk of relapse in 120 children with ALL. Multivariate analysis with the Cox's model; cut off point for the height for age z score=−2

Prognostic factor	*Coefficient*	*Standard error*	*Risk of relapse**	*Lower limit*	*Upper limit*	*Likelihood ratio statistic*	*p Value*
Age	0·9392	0·346	2·6	1·3	5·0	6·71	0·01
Risk factor	0·9577	0·374	–	–	–	6·61	0·01
HAZ†	2·109	0·498	8·2	3·1	21·9	14·63	0·00007

*Risk of relapse: lower and upper limits refer to 95% confidence bounds. For the age: children above 8 years old *v* children less than 8 years; for the height for age z score: children with $z<-2$ *v* children with $z>-2$. Risk factor was included in the model as a continuous variable and so there is no sense in calculating the risk of relapse between groups.
†HAZ: height for age standardised normal deviate z score.

Immunophenotyping was done only in a limited number of patients and cytogenetics was not feasible at the time of diagnosis. The higher prevalence of white cell counts over 50×10^9/l and of PAS negative lymphoblasts suggest that there might be differences in the relative frequencies of immunological and genetic subtypes in developing countries. It would be very interesting to analyse the effect of malnutrition on the rate of relapse adjusted for these factors and we are trying to perform these studies in all new ALL patients.

Previous studies dealing with the influence of socioeconomic factors on the prognosis of ALL suggest the impact of malnutrition on the relapse rate might be explained by the following mechanisms.[5–9] (1) Dose intensity of maintenance drugs. Mexican investigators demonstrated that undernourished children received only approximately 50% of the planned cumulative dose of 6-mercaptopurine, methotrexate, and anthracyclines over 30 months of treatment.[9] The development of granulocytopenia and/or thrombocytopenia led to either withdrawal of the drugs or a decrease of the dose in 68% of undernourished children compared with only 11% of those with a normal nutritional status. (2) Differences in the metabolism of administered drugs: Canadian researchers demonstrated that children given the same mean doses of 6-mercaptopurine and methotrexate during maintenance chemotherapy had different systemic exposure to oral 6-mercaptopurine, measured by the mean area under the mercaptopurine concentration-time curve achieved by a dose of 1 mg/m^2 of body surface area. Children who relapsed had mean (SEM) 1636 (197) nmol/l×minutes as compared with 2424 (177) nmol/l×minutes in those who did not ($p<0{\cdot}005$).[29] (3) Physicians' inability or failure to adhere to the doses recommended by the treatment protocol: in 76 standard risk Canadian children with ALL who were followed up for at least five years from diagnosis, 20 children received less than 60% of the recommended dose of methotrexate; 11 relapsed. Of the remaining 56 children who received more than 60% methotrexate, only 16 relapsed ($p<0{\cdot}05$).[30] It is conceivable that physicians caring for undernourished children might not have increased the dose of maintenance drugs to the maximum tolerated, as recommended by the protocol. (4) Child's or family's non-compliance with treatment: the plasma concentration of 6-mercaptopurine in 17 American children with ALL who allegedly had received the drug two to four hours before blood collection was not detectable in nine out of 27 outpatients visits. After taking the drug under medical supervision, all children had detectable plasma concentrations.[31] In another study, of 22 British children supposedly taking a constant dose of 6-mercaptopurine over a long period, six showed wide variations in the concentration of red cell 6-thioguanine nucleotides. Two children admitted failing to take their tablets and partial non-compliance was probable in at least three others.[32] Undernourished children come from families with low social and cultural level; non-compliance may be common in this setting.[5]

We conclude that malnutrition should be included as a risk factor for ALL relapse in children from developing countries and social groups with relevant nutritional deficits. Its effect is apparently independent of other prognostic variables. The major influence of the nutritional indicator, height for age, suggests that social deprivation may play an important part in the outcome of these children, but there may also be an adverse influence of malnutrition itself on drug metabolism.

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