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Predictors of outcome and methodological issues in children with acute lymphoblastic leukaemia in El Salvador

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ABSTRACT

Background: Most children with cancer live in low-income countries (LICs) where risk factors in paediatric acute lymphoblastic leukaemia (ALL) developed in high-income countries may not apply.

Methods: We describe predictors of survival for children in El Salvador with ALL. We included patients <16 years diagnosed with ALL between January 2001 and July 2007 treated with the El Salvador–Guatemala–Honduras II protocol. Demographic, disease-related, socioeconomic and nutritional variables were examined as potential predictors of event-free survival (EFS) and overall survival (OS).

Results: 260/443 patients (58.7%) were classified as standard risk. Standard- and high-risk 5-year EFS were 56.3 ± 4.5% and 48.6 ± 5.5%; 5-year OS were 77.7 ± 3.8% and 61.9 ± 5.8%, respectively. Among standard-risk children, socioeconomic variables such as higher monthly income (hazard ratio [HR] per $100 = 0.84 [95% confidence interval (CI) 0.70–0.99; $P = 0.04$]) and parental secondary education (HR = 0.49, 95% CI 0.29–0.84; $P = 0.01$) were associated with better EFS. Among high-risk children, higher initial white blood cell (HR per 10×10^9/L = 1.03, 95% CI 1.02–1.05; $P < 0.001$) predicted worse EFS; socioeconomic variables were not predictive. The difference in EFS and OS appeared related to overestimating OS secondary to poor follow-up after abandonment/relapse.

Conclusion: Socioeconomic variables predicted worse EFS in standard-risk children while disease-related variables were predictive in high-risk patients. Further studies should delineate pathways through which socioeconomic status affects EFS in order to design effective interventions. EFS should be the primary outcome in LIC studies.

1. Introduction

In high-income countries (HICs), over 80% of children with acute lymphoblastic leukaemia (ALL) are cured.[1,2] Unfortunately, cure rates are inferior in low-income countries (LICs), where the majority of children with cancer reside.[3] Various phenomena may account for this survival gap, including more treatment toxicity, higher rates of relapse and abandonment of therapy in LICs.

Improvement in survival in HICs has been dependent on the identification of clinical and biological predictors of outcome and the development of various risk stratification schemas.[4]

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This in turn has allowed the tailoring of treatment intensity to disease aggressiveness, avoiding both over and under treatment of individual patients. The success of this approach has resulted in several traditional adverse prognostic factors losing their predictive power in the context of modern treatment.[1,2]

Risk stratification systems developed in HICs may not, however, be appropriate for children with ALL in LICs. Several routine risk factors, such as cytogenetics and minimal residual disease are not commonly available in low-income centres. In addition, differences in underlying biology and external circumstances are likely to require the adaptation of traditional risk strata. Socioeconomic and nutritional factors may also play important roles.

Finding accurate predictors of outcome is essential if LICs are to close the survival gap which currently exists in ALL. The appropriate balancing of treatment intensity to risk of relapse and treatment-related mortality (TRM) is of particular importance in LICs given significant resource constraints and difficulties in supportive care.[5] Despite this, few investigators have systematically examined risk factors for survival in paediatric ALL in LICs. The primary objectives of this study were therefore to determine predictors of event-free survival (EFS) in children with ALL treated in El Salvador, a LIC. The secondary objectives were to describe overall survival (OS) and the relationship between EFS and OS in this population.

2. Materials and methods

2.1. Data source

Data were obtained from two sources. The primary source of data was the Paediatric Oncology Networked Database (POND) (www.pond4kids.org). POND is an online database for paediatric cancer patient information designed to permit users at multiple locations to store and analyse data that include patient demographics, diagnoses, treatments and outcomes in a secure environment with stringent control of access and privacy.[6] Although data collection is primarily to assist in patient outcome monitoring and quality improvement initiatives, data also can be anonymized for research purposes. In El Salvador, two data managers abstract information from patient charts in real time and data are confirmed by the treating oncologists. Routinely collected information includes data on patient demographics, nutrition, socioeconomic status, diagnosis, treatment, complications and outcomes. A similar data management program was initiated in Honduras, where recent audits of POND data quality showed that accuracy for basic data fields was 99%.[6] The second source of data was a separate local electronic database which contained several additional socioeconomic variables; these were collected by the treating oncologists.

2.2. Study population and setting

The patient sample consisted of children diagnosed with ALL and treated with the El Salvador–Guatemala–Honduras II protocol (EGH II) at the Benjamin Bloom National Children's Hospital, San Salvador, El Salvador. This hospital is the sole centre for paediatric oncology in the country and diagnoses approximately 200 new cancer cases a year. We included those age 0–16 years at diagnosis with *de novo* ALL and who were diagnosed between January 1, 2000 and July 1, 2007. Patients with mature B-cell leukaemia were excluded.

Patients with ALL were treated according to the EGH II protocol, which was based on the St. Jude Total XIII and XV protocols.[2,7] Important modifications from the St. Jude protocols included the use of only two risk groups, standard and high. Standard risk patients were defined as those age 1–10 at diagnosis, presenting white blood cell (WBC) count $<50 \times 10^9$/L, DNA index 1.16–1.6 and the absence of any high risk features [central nervous system (CNS) or testicular involvement, T-cell immunophenotype, M3 marrow on day 15, or M2/M3 marrow on day 36]. Etoposide was omitted and the dosing of high dose methotrexate was modified to a 3 h infusion of 2 g/m^2 for standard-risk and 3 g/m^2 for high-risk patients.

The oncology unit at the Benjamin Bloom hospital has 30 inpatient beds: two single rooms and seven rooms with four beds each. Programs targeting hand washing and central line infections were in place during the study period. All children with febrile neutropenia were admitted and started on broad-spectrum antibiotics. Patients received co-trimoxazole for *Pneumocystis jiroveci* prophylaxis. Eighty percent of blood products requests were met expeditiously; the rest were met within 24 h.

Abandonment of therapy is a significant treatment challenge in many LICs and can represent the most common cause of treatment failure.[8] In El Salvador, social workers attempted to contact families who abandoned therapy in order to encourage the resumption of treatment. This often involved visits to the patient's community and home. Treatment was provided at no financial cost to families; accommodation and child care were also offered free to families living significant distances from the treatment centre. This was funded primarily through the support of local non-governmental organisations and international partnerships. These efforts resulted in a decrease in therapy abandonment rates, though significant challenges remain.[9]

2.3. Outcome measures

The primary outcome was EFS, defined as the time from diagnosis to first event or last contact. Events were defined as resistant disease, relapse, second malignant neoplasms, abandonment, or death as a first event. For analytical purposes, resistant disease and second malignancies were combined with relapses when examining event type. TRM was defined as death unrelated to refractory or progressive disease occurring before first remission was achieved, or any death in complete remission. Abandonment of therapy was defined as 4 weeks of missed appointments during active treatment. Though the length of abandonment considered clinically significant will vary between malignancies, a length of 4 weeks has been accepted previously in order to allow comparisons across protocols.[10] OS was defined as the time from diagnosis to death or last contact.

2.4. Potential predictors

Several variables were examined as potential predictors of EFS. These were categorised as biologic, socioeconomic, and

nutritional. Biologic variables included demographic features such as age, sex, and disease-related features such as initial WBC count and uric acid, DNA index, presence of a mediastinal mass at diagnosis and CNS status (for high risk patients). Socioeconomic variables included monthly income, time to travel to clinic, maximal parental education (secondary level or greater versus primary level or lower), presence of a household telephone and mode of transport to clinic (bus versus own transport). Nutritional variables included body mass index percentile, triceps skin fold thickness percentile, mid-upper arm circumference percentile and initial albumin. Body mass index percentile was calculated relative to growth charts published by the Centers for Disease Control and Prevention in 2000.[11] Triceps skin fold thickness provides a measure of fat mass while mid-upper arm circumference is a measure of lean mass and have been previously suggested to be 'gold standard' measures of nutritional status both in general paediatric and oncologic populations.[12] Both were calculated with reference to previously collected population norms.[13]

2.5. *Statistical methods*

Both EFS and OS were described using the Kaplan–Meier method and consisted of time from diagnosis to event/death or last contact. EFS and OS were compared between high and standard risk patients using the log rank test. The proportion of events due to specific causes was compared between risk cohorts using the Chi square test. Univariate and multivariable Cox proportional hazards models were used to explore predictors of EFS stratified by risk strata. Variables with a P value <0.05 on univariate analysis were examined in the multiple regression models. Statistical analyses were performed using SAS-PC software (version 9.2; SAS Institute, Cary, NC) or the Statistical Package for Social Sciences for Windows (version 10.1; SPSS; Chicago, IL). Statistical significance was defined as $P < 0.05$. The study was approved by the research ethics boards at The Hospital for Sick Children in Toronto Canada and the Benjamin Bloom National Children's Hospital in San Salvador, El Salvador. Written informed consent was obtained from all participants.

3. Results

The study sample included 443 children with ALL treated according to the EGH II protocol. Two hundred and sixty (58.7%) were classified as standard risk with the remainder classified as high risk. Demographic characteristics of the patient population can be seen in Table 1.

The 5 year EFS was 56.3 ± 4.5% and 48.6 ± 5.5% for the standard and high risk cohorts, respectively. The 5 year OS was 77.7 ± 3.8% and 61.9 ± 5.8% for standard and high risk patients (Fig. 1). There were 82 events among standard risk children and 74 events among those classified as high risk (Table 2). The proportion of events attributable to specific causes (relapse, TRM, abandonment) was not significantly different between the standard and high risk groups.

Table 1 – Patient demographic characteristics by risk strata.

Characteristic	Standard risk (n = 260)	High risk (n = 183)
Biologic		
Male gender, N (%)	138 (53.1)	109 (60.0)
Age (years), median (IQR)	4.6 (2.4, 7.0)	7.1 (3.3, 10.4)
CNS positive, N (%)	–	8 (4.5)
Immunophenotype, N (%)		
B-Lineage	257 (100.0)	144 (80.9)
T-Lineage	–	34 (19.1)
DNA index, median (IQR)	1.00 (1.00, 1.18)	1.00 (1.00, 1.08)
Initial WBC (10^9/L), median (IQR)	7.8 (3.9, 18.5)	56.0 (10.2, 109.1)
Initial uric acid (μmol/L), median (IQR)	260 (200, 350)	330 (240, 430)
Initial mediastinal mass, N (%)	4 (1.5)	26 (14.2)
Socioeconomic		
Parental education, N (%)		
Illiterate	8 (3.1)	8 (4.4)
Primary	167 (65.2)	111 (61.3)
Secondary	56 (21.9)	43 (23.8)
Advanced	22 (8.6)	18 (9.9)
Transport by bus, N (%)	242 (96.0)	170 (95.5)
Telephone, N (%)	83 (34.2)	71 (40.8)
Monthly income (dollars), median (IQR)	150 (100, 250)	150 (100, 250)
Hours to travel to clinic, median (IQR)	2 (1, 3)	2 (1, 3)
Nutritional		
Initial albumin (g/L), median (IQR)	35 (32, 39)	35 (31, 38)
Body mass index percentile, median (IQR)	41 (10, 79)	50 (15, 88)
Triceps skin fold thickness percentile, median (IQR)	17.5 (2.5, 37.5)	37.5 (7.5, 62.5)
Mid-upper arm circumference percentile, median (IQR)	5.0 (2.5, 25.0)	10.0 (2.5, 50.0)

Abbreviations: CNS – central nervous system; IQR – interquartile range; N – number; WBC – white blood count.

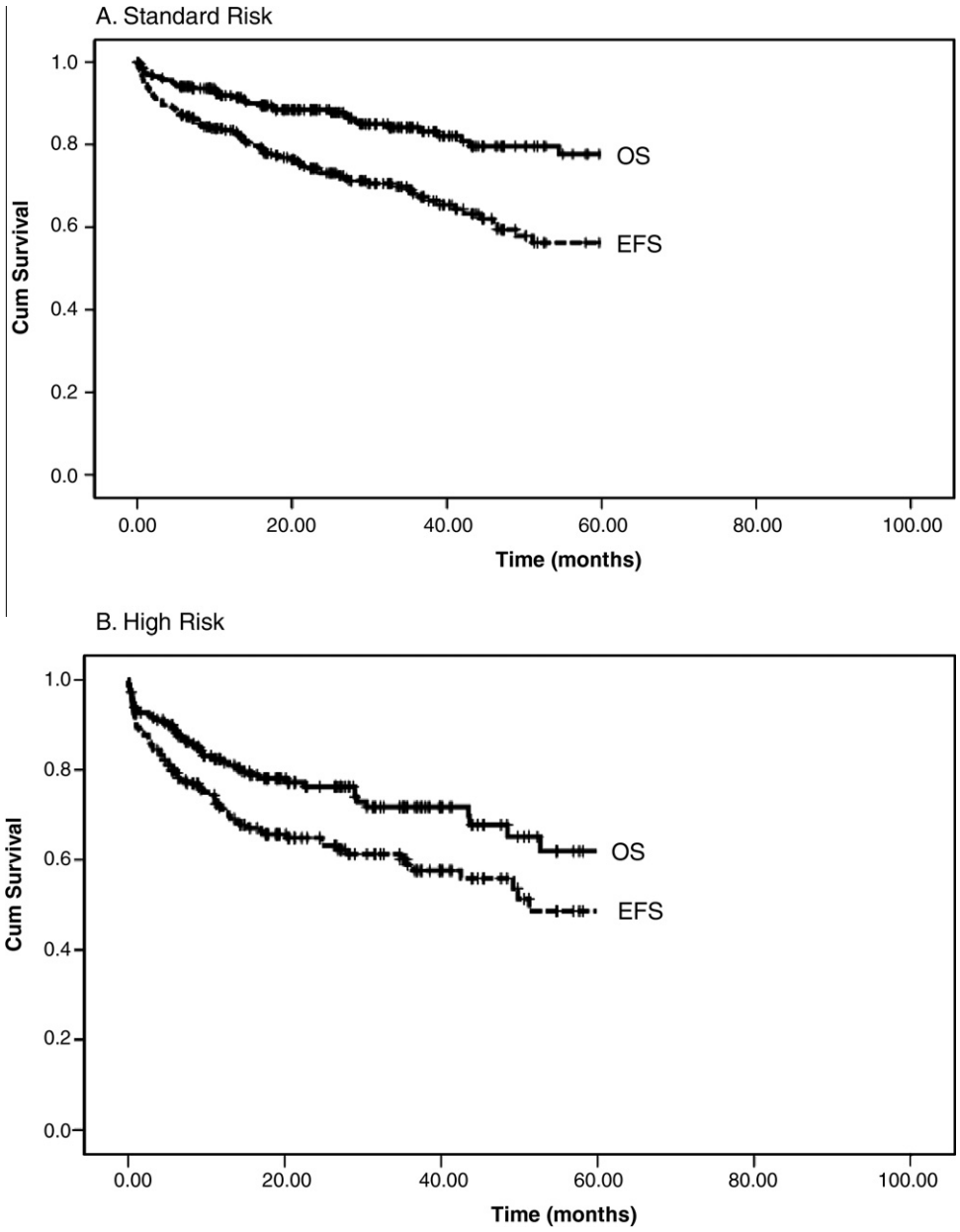

Fig. 1 – Overall and event-free survival for children with acute lymphoblastic leukaemia stratified by risk strata.

Table 2 – Percentage of events attributable to specific causes stratified by risk strata.

Categories	Standard risk	High risk	*P* value
Total number of events	82	74	
Events attributable to specific causes			0.07
Relapse, *N* (%)	33 (40.2)	39 (52.7)	
Treatment related mortality, *N* (%)	16 (19.5)	18 (24.3)	
Abandonment of therapy, *N* (%)	33 (40.2)	17 (23.0)	

Table 3 shows the univariate analyses for predictors of EFS. In the standard risk cohort, socioeconomic variables such as parental secondary education ([hazard ratio (HR) = 0.49; 95% confidence interval (CI) 0.29, 0.84; $P = 0.01$]) and higher monthly income (HR per \$100 = 0.84; 95% CI 0.70, 0.99; $P = 0.04$) predicted better EFS, while longer travel time to clinic (HR per hour = 1.06; 95% CI 1.01, 1.10; $P = 0.01$) predicted worse EFS. The only biologic variable to predict better EFS was higher DNA index (HR = 0.02; 95% CI 0.00, 0.28; $P = 0.003$). In contrast, among high risk children, only disease-related features such as higher WBC at diagnosis (HR per 10×10^9/L = 1.03; 95% CI 1.02, 1.05; $P < 0.001$) and higher initial uric acid (HR per 60 μmol/L = 1.09; 95% CI 1.02, 1.16; $P = 0.01$) were significantly associated with poorer EFS; socioeconomic variables were not predictive. Nutritional variables did not predict EFS among either standard or high risk patients.

Among standard risk children, monthly income and parental education were highly correlated (Spearman correla-

Table 3 – Univariate analysis of biological, socioeconomic and nutritional variables as predictors for event-free survival stratified by risk group.

Factors	Standard risk			High risk		
	HR	95% CI	*P* value	HR	(95% CI)	*P* value
Biologic						
Male	0.82	(0.53, 1.27)	0.37	1.00	(0.62, 1.61)	0.99
Age	0.99	(0.91, 1.09)	0.88	0.96	(0.90,1.02)	0.20
CNS positive	–	–	–	1.34	(0.49, 3.69)	0.57
DNA index	0.02	(0.00, 0.28)	0.003	0.66	(0.13, 3.46)	0.62
Initial WBC (per 10×10^9/L)	1.11	(0.93, 1.31)	0.26	1.03	(1.02, 1.05)	< 0.001
Initial uric acid (per 60 μmol/L)	1.06	(0.98, 1.14)	0.15	1.09	(1.02, 1.16)	0.01
Initial mediastinal mass	1.05	(0.15, 7.55)	0.96	1.70	(0.93, 3.11)	0.08
Socioeconomic						
Parental secondary education	0.49	(0.29, 0.84)	0.01	0.69	(0.42, 1.14)	0.15
Transport by bus	2.32	(0.57, 9.45)	0.24	5.50	(0.76, 39.78)	0.09
Telephone	0.61	(0.36, 1.03)	0.07	0.70	(0.43, 1.16)	0.17
Monthly income (per $100)	0.84	(0.70, 0.99)	0.04	0.91	(0.80, 1.03)	0.14
Time to travel to clinic (per hour)	1.06	(1.01, 1.10)	0.01	1.10	(0.92, 1.31)	0.31
Nutritional						
Initial albumin (per 10 g/L)	0.77	(0.48, 1.21)	0.26	0.94	(0.60, 1.45)	0.77
Body mass index percentile	1.00	(0.99, 1.01)	0.89	1.00	(0.99, 1.01)	0.75
Triceps skin fold thickness percentile	1.00	(0.99, 1.02)	0.90	0.99	(0.98, 1.01)	0.38
Mid-upper arm circumference percentile	0.98	(0.96, 1.01)	0.22	1.00	(0.99, 1.01)	0.89

Abbreviations: CI – confidence interval; CNS – central nervous system; HR – hazard ratio; WBC – white blood count.

Table 4 – Length of follow-up in months among children not known to have died stratified by risk group.

Factors	Standard risk			High risk		
	N	Post diagnosis*	Post event	*N*	Post diagnosis*	Post event
Follow-up time among those who relapse, median (IQR)	22	38 (19, 58)	8 (3, 18)	20	22 (15, 48)	4 (3, 10)
Follow-up time among those who abandon therapy, median (IQR)	22	13 (2, 24)	0 (0, 15)	9	4 (2, 21)	0 (0, 0)
Follow-up time among those with no event, median (IQR)	178	30 (17, 45)	–	108	28 (15, 41)	–

Abbreviation: IQR – interquartile range.

* Comparison of total follow-up time post diagnosis significantly different among those who relapse, abandon therapy and with non-event in both standard risk ($P = 0.002$) and high risk ($P = 0.001$) groups.

tion coefficient = 0.47, $P < 0.001$); only parental education was therefore included in the multiple regression model. When parental education, travel time to clinic and DNA index were placed in the multivariable model, each remained independently predictive of EFS (parental secondary education adjusted HR = 0.55, 95% CI 0.31, 0.97; $P = 0.04$; travel time to clinic adjusted HR per hour = 1.06, 95% CI 1.02, 1.11; $P = 0.007$; DNA index adjusted HR = 0.02, 95% CI 0.00, 0.03; $P = 0.004$). Among high risk children, initial WBC and initial uric acid were highly correlated (Spearman correlation coefficient = 0.41, $P < 0.001$); therefore multiple regression was not conducted in this strata.

Given the considerable gap between the 5 year EFS and OS curves in both standard and high risk cohorts, we examined the length of both total and post-event follow-up for patients experiencing relapse or abandonment as a first event, excluding those children who were known to have died (Table 4). The median length of follow-up after a relapse was 8 months [interquartile range (IQR) = 3–18 months] for children of standard risk and 4 months (IQR = 3–10 months) for high risk children. For children who abandoned therapy but not known to have died, the median length of follow-up post event was 0 months (IQR = 0–15 months) and 0 months (IQR = 0–0 months) for standard and high risk patients, respectively.

4. Discussion

This study found that among children with ALL treated in El Salvador, the 5 year EFS was 56.3 ± 4.5% and 48.6 ± 5.5% for the standard and high risk patients, while the 5 year OS was 77.7 ± 3.8% and 61.9 ± 5.8%. Among the standard risk cohort, socioeconomic variables predicted EFS, while only disease-related variables did so in high risk children.

One striking finding is the wide and sustained gap between EFS and OS in both standard and high risk patients. In HICs, this difference is usually indicative of successful

salvage regimens. In this context of this study, this would represent the salvage of children who relapse and the successful re-treatment of children who abandon and return. Clinically however, we know that the probability of salvage following relapse or abandonment of therapy should be low. We therefore undertook further analyses and found that the median follow-up after relapse or abandonment in children not known to have died was only 0–8 months, depending on the specific event and risk cohort. The gap between EFS and OS found in El Salvador is therefore highly unlikely to be due to salvage, but instead to methodological issues unique to LICs. Families who abandon therapy as a first event may or may not return to seek future treatment, and families of children who relapse may be more prone to abandoning further therapy. This implies that in LICs with an appreciable abandonment rate, EFS should be the major measure of outcome. In addition, further investigation into the course of LIC children who relapse or abandon therapy is clearly needed. The role of routine follow-up in LICs must also be improved before overall survival can be considered a meaningful outcome in this context.

In HICs, significant effort has gone into the identification of predictors of outcome. Traditional prognosticators such as age, WBC count, immunophenotype and response to therapy have been joined by cytogenetics and MRD, and have formed the basis of current risk stratifications on which treatment intensity is determined.[1,4,14–17] With the use of modern treatment protocols, some of these variables may have lost predictive significance.[1,2] By comparison, the effect of socioeconomic status on outcome in HICs has been far less studied and the results have been conflicting.[18–20]

In LICs, relatively few studies have examined predictors of outcome in ALL. In one Chinese study, age, induction failure and the presence of the Philadelphia chromosome remained independent predictors of EFS.[21] In India, Advani and colleagues found increased WBC, lowered haemoglobin and lymphadenopathy to be unfavourable predictors of EFS.[22] Interestingly, in that population, demarcation according to the National Cancer Institute criteria did not distinguish between groups with different EFS, suggesting that the prognostic value of even age and initial WBC may vary from context to context.

Measures of socioeconomic status such as urban/rural residence, income and education have been shown to predict survival in childhood ALL in LICs such as China and Indonesia.[23,24] In both these contexts, families were mainly responsible for the financial burden of treatment. In one Brazilian study, where treatment was free, socioeconomic status (determined predominantly by income) was a significant predictor of survival independent of nutritional status.[25] Various mechanisms underlying this association have been suggested, including an inability to absorb opportunity costs, poor understanding of the disease, differential attitudes and practices of health care providers and poor compliance.[24,26–28]

In our study, in which a wide range of demographic, disease-related, socioeconomic and nutritional variables were examined as potential predictors of EFS, socioeconomic variables were the major predictors of EFS in standard risk children. It is again worth noting that this association was found despite the provision of free treatment to all patients. In high risk patients however, only disease-related variables predicted EFS. Several explanatory mechanisms for this differential risk profile are possible. On one hand, standard and high risk cohorts may have different proportions of specific events, each with its own predictive variables; our inability to demonstrate such differences may reflect inadequate power. Prior work by our group, however, has shown that socioeconomic variables predict the risk of both TRM in acute leukaemia and of abandonment among a general paediatric oncologic population.[9,28] Different ratios of specific events are therefore unlikely to be the sole reason for the difference in predictors of survival. Alternatively, in high risk children, a combination of biologically aggressive disease and more intense treatment may overwhelm any protective effect of socioeconomic status. Although an early study found an association between socioeconomic status and outcome in ALL, with the strongest association in low risk children (those with presenting WBC counts $<30 \times 10^9$/L), most more recent HIC trials have failed to show such an association).[19,29]

Basing future treatment intensity on risk profiles including socioeconomic variables may be risky without knowing the precise underlying mechanisms. For example, increasing treatment intensity for patients of low socioeconomic status based on prior poor outcomes may result in even worse EFS given the sizeable TRM rate in both risk groups. Significant side-effects or the burden of more inpatient treatment may also cause higher rates of abandonment. Indeed, the institution of high intensity treatment protocols designed in HICs may cause more harm than benefit. A more rational approach would be to better understand how low socioeconomic status is associated with worse outcomes and target those mechanisms specifically. Interventions targeting TRM and abandonment specifically are justified. Whatever the intervention, simultaneous and rigorous outcome monitoring is essential.

Strengths of this study include the population-level nature of the analysis and the diversity of variables examined. One significant weakness, however, is that our study did not capture those patients who died before reaching the central treatment centre. In addition, LIC centres are likely to differ in terms of their populations, treatments and contexts. The effect of socioeconomic status for example is likely to be magnified in settings where treatment is not provided for free. Our results should therefore be verified in other LIC populations.

In conclusion, among children with ALL in El Salvador, socioeconomic variables predicted worse EFS in standard risk children while disease-related variables were predictive in high risk patients. Elucidation of the mechanisms underlying these associations requires further investigation, though children of standard risk and low socioeconomic status may benefit from targeted supportive programs. OS was significantly higher than EFS, reflecting methodological issues unique to LICs and in particular, inability to obtain follow-up in those who abandon therapy. EFS should therefore be the target outcome measure in future LIC analyses.

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Conflict of interest statement

None declared.

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