



The magnitude and predictors of abandonment of therapy in paediatric acute leukaemia in middle-income countries: A systematic review and meta-analysis

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Abstract Background: Abandonment of therapy is a significant cause of paediatric cancer treatment failure in low- to middle-income countries (LMIC), but its impact has been underestimated. We performed a meta-analysis to determine the magnitude of abandonment in paediatric leukaemia in LMIC and sought to identify patient-, centre- and country-specific predictors of abandonment.

Patients and Methods: We searched seven databases to identify paediatric oncology cohorts followed up from diagnosis and treated in LMIC. All languages were included. Two reviewers independently selected articles and extracted data. Authors were contacted for additional information. Subgroup analyses were planned a priori.

Results: Of 22,384 publications, 318 in eight languages met criteria for full text review. 157 studies met analysis inclusion criteria. Abandonment rates (ARs), obtained for 83 of the 157 studies (52.9%), ranged from 0% to 74.5%. ARs were frequently unreported and available only directly from authors. Forty studies (10,494 children in 20 countries) were quantitatively analysed. ARs for acute lymphoblastic leukaemia in lower-middle-income countries

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(lower-MICs) were higher than in upper-middle-income countries (29%, 95% confidence interval (CI) 23–36% versus 2%, 95% CI 1–3%; $p < 0.0001$) but were heterogeneous ($I^2 = 98\%$; $p < 0.0001$). This heterogeneity was not explained by centre-specific (free versus paid treatment) or country-specific (government health expenditure, per-capital income) subgroups.

Conclusions: In LMICs, ARs are highest in lower-MICs. However, their broad range suggests that low ARs are possible in resource-constrained settings. Analysis of outliers may suggest interventions for use at other centres. Methodologically appropriate reporting of ARs should be adopted. Future research should evaluate interventions targeting abandonment.

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1. Introduction

In high-income countries (HIC), remarkable advances in paediatric oncology have led to cure rates above 80%.¹ This success has not translated to low- and middle-income countries (LMIC), where most children with cancer reside.² The resultant survival gap has been attributed to delayed presentation, greater treatment-related mortality and a higher rate of relapse.³

Another important yet often overlooked cause is abandonment of therapy, the failure to start or complete potentially curative therapy.⁴ Patients who abandon therapy may also be excluded from analyses, leading to underestimations of the impact of abandonment. A previous narrative review on this topic used a narrow search strategy that excluded many studies reporting abandonment.⁵ We therefore conducted a systematic review and meta-analysis with the primary objective of determining the magnitude of abandonment for paediatric acute leukaemia in LMIC. Our secondary objective was to identify predictors of abandonment and to describe outcomes of, reported reasons for, and interventions against abandonment.

2. Patients and methods

2.1. Data sources

We performed electronic searches of Ovid Medline, EMBASE, CINAHL and four regional databases (Index Medicus for the Eastern Mediterranean Region, SciELO, LILACS, African Index Medicus) for the dates from 1st January 2000 to July 2011. As searches focused on abandonment would fail to capture studies on other primary outcomes, we attempted to identify all reports of cohorts of children treated for malignancies in LMIC. The keyword ‘neoplasms’ and country-specific terms were used, and searches were limited to children. The complete Ovid Medline search strategy is shown in [Supplemental Fig. 1](#).

2.2. Study selection

Inclusion criteria were: (1) cohort or randomised controlled trials; (2) paediatric data (<18 years); (3) conduct

in a LMIC, as defined by the World Bank 2009 Gross National Income (GNI) per capita;⁶ (4) the following malignancies: acute lymphoid or myeloid leukaemia, brain tumours, neuroblastoma, Wilms tumour, rhabdomyosarcoma, Ewing sarcoma, hepatoblastoma, retinoblastoma, or germ cell tumour and (5) at least one of the following outcomes: event-free survival (EFS), overall survival (OS), disease-free survival (DFS), treatment-related mortality (TRM), rate of relapse, or abandonment. Exclusion criteria included: (1) patients not followed up from initial diagnosis; (2) patients undergoing stem cell transplantation; (3) primary objective to determine the effectiveness of a surgical technique; (4) <20 patients (to exclude centres treating small numbers of patients); (5) narrative reviews and (6) population-based outcomes (e.g. mortality per 100,000). Selected studies were restricted to those published in full manuscript form. All languages were included.

Each abstract was independently evaluated by two reviewers (S.G. and either S.Y. or A.M.). Any potentially relevant manuscript was retrieved in full and screened independently by two reviewers; discrepancies were resolved through consensus. Non-English, non-Chinese articles were evaluated by one reviewer. This report addresses only abandonment of therapy for paediatric acute leukaemia.

2.3. Data abstraction

Data were independently abstracted by two reviewers, using a standardised data collection form. The primary outcome was the abandonment rate (AR), defined as the percentage of children who either refused to begin potentially curative therapy at diagnosis or who abandoned therapy during active treatment.⁴ Loss to follow-up after relapse or completion of therapy was excluded. As our primary objective was descriptive, study-level bias was determined by whether ARs were reported. We also determined how abandonment was methodologically handled in calculating overall EFS or OS (included as an event, censored or unknown). Studies were also classified by whether their primary objective was to determine the prognostic significance of a genetic or biochemical marker, as the reporting of ARs may be less relevant for these studies.

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