Cancer Epidemiology 39 (2015) 209–215

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

# Family circumstances and survival from childhood acute lymphoblastic leukaemia in West Germany

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ARTICLE INFO

*Article history:*
Received 1 September 2014
Received in revised form 22 January 2015
Accepted 24 January 2015
Available online 17 February 2015

*Keywords:*
Childhood acute lymphoblastic leukaemia
Survival
Family characteristics
Number of siblings
Birth order
Parental age

ABSTRACT

*Background:* Little is known about the relationship between family characteristics and survival from childhood acute lymphoblastic leukaemia (ALL), which we studied for the first time in German children.
*Methods:* ALL cases were diagnosed between 1992 and 1994 and information on family characteristics was collected during a previously conducted nationwide case–control study. Children were followed for 10 years after diagnosis, as few disease-related events occur afterwards. Cox proportional hazards models estimating hazard ratios (HR) were calculated using overall as well as event-free survival methods.
*Results:* Second born children showed statistically significant better survival compared to first or later born children, with HRs ranging between 0.54 and 0.64 compared to firstborns. Somewhat poorer survival was observed for children having 3 or more siblings. A relationship was found for parental age at child's diagnosis, with poorer survival for children with younger parents (≤25 years of age at child's diagnosis), or with older fathers. The HR was statistically significant for fathers being ≥41years of age (HR of 2.1). No relationship between degree of urbanization of the place of residence at diagnosis and ALL survival was observed.
*Conclusion:* Family circumstances may have an impact on survival from childhood ALL in Germany. Further research is warranted to elaborate the relationship of specific family characteristics and ALL survival and to investigate possible differential adherence to therapy and interactions with physicians.


## 1. Introduction

With an annual incidence of 44 per million children, acute lymphoblastic leukaemia (ALL) is the most common malignancy in German children, accounting for over a quarter of all paediatric cancers in Germany [1]. Over the last decades, advances in diagnosis and treatment led to considerable improvements in outcome [2,3], with the five-year survival now exceeding 85% in Germany [1] and most of Europe [4].

Diagnostic procedures and treatment protocols are largely standardized within developed countries [2,3,5–8] including Germany [3,9]. Germany has a dense network of specialized paediatric clinics and health care is free of charge for all children irrespective of the family's social circumstances [10]. Therefore we would expect fairly equal survival rates across social groups and independent of family circumstances and, indeed, a recent study did not observe a relationship between socio-economic background and ALL survival in Germany [11]. However, besides physician's compliance to the treatment protocols, parents' and child's adherence to the treatment and supportive care as well as the interaction between families and physicians may indeed affect survival. Treatment of ALL lasts over several years [3,9], and poor adherence to oral maintenance therapy may have negative impact on cure rates [12]. As soon as the child is discharged from hospital, parents are responsible to comply with the recommendations for continuation of a highly demanding therapy.

From an international perspective, only few studies have investigated the relationship between family and social circumstances and survival from leukaemia, with very diverse observations even within Europe [11,13–20]. As an extension to the study on survival from ALL and the impact of socio-economic background [11] we investigated here for the first time the

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http://dx.doi.org/10.1016/j.canep.2015.01.012
1877-7821/

impact of family circumstances on survival from paediatric ALL in Germany.

## 2. Material and methods

### 2.1. Study population and follow-up

Paediatric ALL was defined as diagnosed at ages younger than 15 years. The study population consists of cases from a former German case–control study, covering all of former West Germany (details published elsewhere [21]). Briefly, cases were identified in the nationwide German Childhood Cancer Registry (GCCR), and eligible if diagnosed between October 1992 and September 1994 and if the child was living anywhere in former West Germany. 82% of the invited case families ($N = 647$) participated in the former case–control [11] study which served as the study population of this follow-up investigation. Information on all family characteristics used in this study was collected by self-administered questionnaire during the original case–control study. Children with ALL were treated according to the treatment protocol of the ALL-BFM 90 [3] or COALL 92 trial [9] during this diagnostic period.

We defined family circumstances by a range of features including parental age, birth order, number of siblings, as well as degree of urbanization of the place of residence, using the official governmental categorization. All characteristics correspond to the situation at the date of child's diagnosis. Birth order and number of siblings were defined by counting all live-births of the same mother.

Active vital status follow-up is conducted routinely by the GCCR [22]. We censored at 10 years follow-up as very few disease-related events occur afterwards but the incidence of competing risks rises. Further information on the follow-up process of the GCCR as well as on adjustment characteristics (e.g. maternal education as indicator of socio-economic status) are published elsewhere [11,22].

### 2.2. Statistical analyses

We defined two primary outcomes for these analyses: overall survival, with death from any cause as the endpoint, and event-free survival, with the first (if any) relapse (defined as >5% lymphoblasts in bone marrow), second malignant neoplasm or death as events. Children were observed for 10 years from the date of diagnosis until the date of event, last date known to be alive, or date of 10 years of follow-up, whichever came first.

For graphical illustration we calculated (unadjusted) survival probabilities stratified by birth order, number of siblings and parental age, using Kaplan–Meier curves. Statistical significance ($p \leq 0.05$) of differences in survival probabilities was assessed by the log-rank test [23].

Cox proportional hazards models were used to assess the impact of selected characteristics applying overall (Models I and II) and event-free survival methods (Models III and IV) [24]. The multiple regression models were built up in two steps. Initially, we adjusted for the well–established prognostic factors age at diagnosis [3] (grouped into <1 year, 1–5 years, 6–9 years, 10–14 years) and sex [25] (Model I and Model III). Model II and Model IV were additionally adjusted for the possible mediating effect of other family variables (*adjustment varied between family characteristics*). Results were expressed as adjusted hazard ratios (HRs) with corresponding 95% confidence intervals.

The proportional hazards assumption for the Cox models, tested using the Schoenfeld residuals test [24], failed for the variable child's age at diagnosis in the category "<1 year" ($N = 26$). Nevertheless, as the hazard ratios changed only marginally when excluding the infants from the analyses, results in this manuscript relate to all subjects combined.

All statistical analyses were performed using Stata 13 [26].

## 3. Results

As expected from German national cancer registry data [1], out of the 647 cases, 60% were boys and almost two thirds were 1–5 years of age at diagnosis (Table 1). Among all cohort members, 334 (52%) were firstborns and 159 (25%) were the only child; almost half of the families of our cohort had two children. With respect to place of residence, most families were living in urban areas, and most parents were aged ≤30 years at diagnosis. Numbers of missing values were very low for the key variables, ranging between 0.5% for maternal age and 1.6% for paternal age.

10-year overall survival was 84.7%, based on 98 deaths. Survival was somewhat better for girls than boys (88% vs. 83%) and age-wise highest for children aged 1–5 years at diagnosis.

Kaplan–Meier curves suggest differences in overall survival from ALL by family characteristics *(although statistically significant only for birth order)* (Fig. 1). Considerably poorer survival is seen for children with 3 or more siblings compared to those with fewer siblings. This dissimilarity appears to emerge about 1.5 years after diagnosis. Regarding birth order, survival was highest for second born children ($p = 0.048$). The relationship of parental age at diagnosis and long-term survival from ALL appears to be U-shaped, with poorer survival for children with younger (*≤25 years*) or older parents (*maternal age ≥36 years, paternal age ≥41 years*) but highest in children of mid-aged parents. This U-shape was particularly pronounced for the associations seen with father's age.

Table 2 displays the results from the multivariate analyses on the impact of family characteristics on overall and event-free survival. The adjusted findings confirm the overall associations observed from the unadjusted survival curves, with also similar patterns found for overall and event-free survival and across models. The group of second born children had a statistically significant better survival compared to first or later born children, with HRs ranging between 0.54 and 0.64 compared to firstborns, depending on the model. The risk of dying of children with 3 or more siblings increased with additional adjustment (*Models II* and *IV*), resulting in a non-significant HR of about 1.6 in the fully adjusted model. Children with one or two siblings showed slightly better survival than their counterparts from single child families. A sensitivity analysis mutually adjusting for birth order and number of siblings pointed towards an even stronger relationship between number of siblings and ALL survival, with increasing HRs with increasing number of siblings in a family. HRs for children with 3 and more siblings exceeded 2.4 (*overall survival*) and 2.7 respectively (*event-free survival*) in the fully adjusted models.

The non-linear relationship of parental age at diagnosis and survival persists in the adjusted analyses. Children with a father aged 41 years or older showed a statistically significant increased HR of 2.1 (95% CI 1.04; 4.20). Likewise, children with a father aged 25 years or younger at child's diagnosis had poorer survival (HR 1.65; 95% CI 0.97; 2.81), although not statistically significant. The relationship was weaker for maternal age and persisted in the fully adjusted models mainly for young mothers (HR 1.33; 95% CI 0.81; 2.19).

A sensitivity analysis distinguishing between having either a young mother or a young father and having two young parents (both ≤25 years) indicated that particularly the latter was related to poorer survival. Elevated HRs of up to 1.76 were found for having both a young mother and a young father.

No relationship between degree of urbanization of place of residence at diagnosis and survival was observed, although HRs for living in a rural area were somewhat lower than 1.