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1 **Long-term survival after childhood acute lymphoblastic leukaemia: population-based**  
2 **trends in cure and relapse by clinical characteristics**

3

4 **Short title:** Trends in childhood ALL cure and relapse

5

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24

1 **Summary**

2 'Cure models' offer additional information to traditional approaches to assess survival for  
3 cancer patients by simultaneously estimating the proportion cured and the survival of those  
4 'uncured'. The proportion cured is a summary of long term survival while the median survival  
5 time of the uncured provides important information on those who are not long-term survivors.  
6 Population-based trends in the cure proportion and survival of the uncured for childhood  
7 acute lymphoblastic leukaemia (ALL) by clinical prognostic risk factors were estimated using  
8 flexible parametric cure models, based on overall survival and event-free survival. Children  
9 aged 1-17 years diagnosed from 1990-2011 in Yorkshire, UK, were included (n=492). The  
10 percentage cured increased from 77% (95%CI 70-84%) in 1990-1997 to 89% (84-93%) in  
11 2003-2011, while the median survival time of the uncured decreased from 3.2 years (2.2-4.1  
12 years) to 0.7 years (0-1.5 years). Models based on event-free survival showed a similar  
13 trend. The 5-year cumulative incidence of relapse substantially decreased from 35% in  
14 1990-97 to 9% in 2003-2011. These results show selective improvement in survival between  
15 1990 and 2011 with a significant reduction in the risk of relapse alongside a reduced  
16 absolute duration of survival for those destined to be uncured.

17

18 **Keywords:** acute lymphoblastic leukaemia, cure, survival, event-free survival

19

## 1 **Introduction**

2 Acute lymphoblastic leukaemia (ALL) is the most frequently diagnosed cancer subtype in  
3 children accounting for 25% of all childhood cancers and 79% of all childhood leukaemias  
4 (Stiller 2007). Five-year survival for ALL has increased substantially since the 1960s and the  
5 EUROCORE-5 study found 5-year survival for children with ALL diagnosed 2000-2007 was  
6 86% (Gatta, et al 2014).

7

8 ALL patients are risk-stratified based on clinical features including white cell count (WCC),  
9 age, sex and more recently cytogenetic data (Moorman, et al 2010, Vora, et al 2013) and  
10 survival differences between risk groups are generally based on clinical trial outcomes.

11 Although recruitment into clinical trials for children with ALL in the UK is high, estimated  
12 between 85-99% for children (Stiller, et al 2012, van Laar, et al 2015) and 66-77% for those  
13 aged 15-17 years (Hough, et al 2017), survival estimates based on clinical trial outcomes for  
14 ALL are not population-based. ALL patients enrolled into clinical trials have been shown to  
15 have a survival advantage compared to those not enrolled on trials (Hough, et al 2017,  
16 Strahlendorf, et al 2018). Population based studies on long-term ALL survival, including  
17 clinical risk factors, are needed to provide real-world benchmark estimates of prognosis.

18

19 Standard statistical methods to assess cancer survival generally analyse all patients as one  
20 group. A statistical cure model offers an alternative approach to provide additional insights  
21 into survival trends by assuming there are two groups of patients: one who do not  
22 experience the outcome of interest and are 'cured' and the other who do experience the  
23 outcome (the 'uncured') and their survival is estimated separately (Lambert, et al 2007,  
24 Othus, et al 2012, Sposto 2002). Cure is measured at the population level and is defined as  
25 the proportion of patients as a group for whom there is no excess mortality compared to the  
26 general population. The proportion cured is an estimate of long-term survival but cure  
27 models also allow the survival of patients who are not long-term survivors to be investigated.  
28 Covariates may have different association with patients who are cured and those who are

1 not. Furthermore, they are useful when investigating temporal trends in survival. For  
2 example, if survival has increased over time, cure models can provide additional information  
3 on whether this was because the proportion of patients cured over time increased, or  
4 because the survival time of those patients who will eventually die increased or a  
5 combination of both (Verdecchia, et al 1998, Yu, et al 2013).

6  
7 Cure models have previously been applied to children with ALL and found that the proportion  
8 of children cured has increased steadily since the 1970s (Gatta, et al 2013, Shah, et al  
9 2008). However, they have not been utilised to describe either population-based trends in  
10 'uncured' individuals or event-free survival or estimate the proportion cured by clinical  
11 prognostic risk factors. Furthermore, estimates of the proportion cured have not been  
12 reported for children with ALL diagnosed since 2002.

13  
14 The aims of this study were to utilise population-based data to estimate the cure proportion,  
15 trends in event-free survival and median survival of the uncured in children diagnosed with  
16 ALL between 1990 and 2011, including trends by clinical risk stratification variables including  
17 cytogenetic risk group.

18

## 19 **Materials and Methods**

### 20 **Study population**

21 Data were extracted from the Yorkshire Specialist Register of Cancer in Children and Young  
22 People (YSRCCYP), a population-based database of children and young people (0-29  
23 years) diagnosed with cancer residing in the Yorkshire and Humber region in the north of  
24 England, covering a population of approximately 2 million 0-29 year olds. The primary  
25 source of ascertainment was hospital records with secondary sources including  
26 neuropathology reports, hospital admissions and other regional and national cancer  
27 registries (van Laar, et al 2010). All patients were proactively followed-up every two years to  
28 ascertain their vital status with minimal loss to follow-up. Relapse information is received

1 through direct notifications from the cancer centre and via the biennial follow-up of patients.  
2 The YSRCCYP has ethical approval from the Northern and Yorkshire Multi Centre Research  
3 Ethics Committee (MREC) and approval under section 251 of the NHS Act (2006) for holding  
4 identifiable patient data from the Health Research Authority Confidentiality Advisory Group.

5

6 We identified all patients diagnosed with acute lymphoblastic leukaemia (ALL),  
7 corresponding to the International Classification of Childhood Cancer 3<sup>rd</sup> Edition group Ia  
8 (Steliarova-Foucher, et al 2005), between October 1990 and June 2011 aged 1-17 years  
9 (before 18<sup>th</sup> birthday) (to coincide with the availability of national ALL clinical trials). This age  
10 range was included rather than the commonly used childhood age range 0-14 years, as it  
11 reflects the paediatric age range treated in clinical practice at the hospitals in the study  
12 region. This was also the upper age limit of the UKALL 2003 trial which opened in 2003  
13 although this increased to 20 years in 2006 and to 24 years from 2007 onwards (Vora, et al  
14 2013); 18-24 year olds have been excluded from this study as they were treated on different  
15 protocols prior to 2006.

16

17 Relapse was defined as recurrent disease either occurring locally at the same site as the  
18 initial diagnosis and/or elsewhere (Feltbower, et al 2007). The exact date of relapse was  
19 extracted for analysis.

20

21 Trends over time were assessed using three time periods corresponding to the recruitment  
22 periods of the three main trials for ALL in the UK: UKALL XI from October 1990 to March  
23 1997 (Hann, et al 2001), ALL97 and ALL97/99 from April 1997 to September 2003 (Mitchell,  
24 et al 2009, Mitchell, et al 2005, Vora, et al 2006) and UKALL2003 from October 2003 to June  
25 2011 (Vora, et al 2013). Within the ALL 97 trial, the duration and treatment intensity changed  
26 in November 1999 (with this phase known as ALL97/99) (Mitchell, et al 2009), however we  
27 were unable to consider these two separated by sub-period due to sample size restrictions.

28

1 Patient sex, age at diagnosis (1-9 years,  $\geq 10$  years) and white blood cell count (WCC) at  
2 diagnosis ( $< 50 \times 10^9/L$ ,  $\geq 50 \times 10^9/L$ ) were extracted from the database and included as  
3 prognostic risk factors as these are used in clinical practice for risk stratification (Vora, et al  
4 2013). Patients with missing WCC were excluded from analysis (n=26, 5%).

5

6 For a subset of patients recruited into clinical trials we obtained their cytogenetic risk group  
7 via linkage to the Leukaemia Research Cytogenetics Group database. Patients were  
8 matched on personal identifiers including NHS number, patient names, date of birth and sex.  
9 Cytogenetic risk group was coded as good, intermediate or poor for B-cell precursor ALL  
10 and all T-cell precursor ALL were included in one group (Moorman, et al 2010). For some  
11 patients after linkage we were unable to obtain their risk group (categorised as "Unknown").  
12 The characteristics of patients with and without cytogenetic data are shown in  
13 supplementary table 1.

14

15 All cases were followed-up to 31<sup>st</sup> December 2016, providing at least 5 years follow-up for  
16 each patient. Overall survival (OS) was defined from date of diagnosis to date of death or  
17 censoring. Event-free survival (EFS) was defined from date of diagnosis to date of relapse or  
18 date of death, whichever occurred first.

19

## 20 **Statistical methods**

21 Overall survival and EFS were examined by prognostic risk factors (period of diagnosis, age,  
22 sex, WCC and cytogenetic risk group) and graphically by Kaplan Meier survival curves.

23

24 Flexible parametric cure models were used to estimate the proportion cured and the median  
25 survival of the uncured (Andersson, et al 2011). Models were based on both overall survival  
26 and EFS. Models based on overall survival were modelled in the relative survival framework.  
27 Relative survival is defined as the observed survival divided by the expected survival where  
28 the expected survival is obtained from national life tables stratified by age, sex and calendar

1 year. If the relative survival function reaches a plateau at some point after diagnosis then the  
2 excess hazard is zero and the cancer patients still alive experience the same survival as the  
3 general population and are considered statistically cured. The median survival time (MST) of  
4 the 'uncured' was estimated simultaneously from the model. The proportion cured provides  
5 an estimated of long term survival while the MST of the uncured which gives information on  
6 those who are not long-term survivors.

7

8 Covariates were included as time varying coefficients so that the proportion cured and the  
9 survival function of the uncured varied by covariates. Excess mortality rate ratios (EMRR),  
10 which are equivalent to the hazard ratio from a Cox model, were estimated from the cure  
11 model and allow the examination of the association of covariates on survival and cure.

12 Models for overall survival were fitted in the relative survival framework using national  
13 lifetables for England obtained from the Office for National Statistics (Office for National  
14 Statistics 2017).

15

16 Each risk factor (period of diagnosis, age, sex and WCC) was included in a univariable  
17 model and a fully adjusted model including all the covariates. The cure model provides  
18 estimates separately for each combination of covariates in the model, therefore to make  
19 comparisons between levels of each covariate while adjusting for the others we calculated  
20 standardised estimates (Andersson, et al 2014, Eriksson, et al 2016). For example, the cure  
21 proportion for each sex was estimated assuming that the distribution of the other covariates  
22 (age, period of diagnosis and WCC) was the same as the whole study population.

23 Standardised estimates were calculated for both the cure proportion and MST for both  
24 overall survival and EFS. All survival estimates and the proportion cured are presented as  
25 percentages rather than proportions.

26

27 Sensitivity analysis was conducted to compare results from the cure model to a survival  
28 model without the assumption of 'cure'. Univariable and multivariable flexible parametric

1 survival models (Royston and Lambert 2011) were included for each risk factor as described  
2 above.

3  
4 Further cure models including cytogenetic risk group were estimated, including those with  
5 unknown cytogenetic risk group and those we were unable to link as separate categories.

6  
7 The cumulative incidence of relapse was estimated by time period with death as a  
8 competing risk (Coviello and Boggess 2004).

9

## 10 **Results**

11 A total of 492 patients were included, of whom 81 (17%) died and 90 (18%) relapsed within  
12 the follow-up period (Table 1). The median time from diagnosis to relapse was 2.5 years  
13 among relapsing patients and 53% (n=48) died during follow-up. Relapsing patients had a  
14 median overall survival of 3.9 years. Cytogenetic data was available for 417 (85%) patients  
15 and of these 38 (9%) were included in the unknown risk group. After excluding the unknown  
16 and not linked group (n=379 remaining), 183 (48%) patients were in the good risk group, 124  
17 (33%) in the intermediate risk group, 24 (6%) in the poor risk group and 48 (13%) had T-cell  
18 ALL.

19

20 Five-year relative survival increased slightly from 86% (95% confidence interval (CI) 79, 91)  
21 in 1990-1997 to 89% (95%CI 84, 93) in 2003-2011, while there was a significant increase in  
22 5-year EFS over the same period from 62% (95%CI 53, 69) to 86% (95%CI 81, 91%)  
23 (Tables 2 and 3, Figure 1). The survival curves tended to flatten out around 8-10 year after  
24 diagnosis.

25

26 For relative survival, the adjusted excess mortality rate ratio (EMRR) was 55% lower in  
27 2003-2011 compared to 1990-97 (Adjusted EMRR=0.45 (95%CI 0.26, 0.80), table 2). The  
28 standardised percentage cured increased from 77% (95%CI 70, 84%) in 1990-97 to 89%

1 (95%CI 84, 93%) in 2003-2011 while the median survival of the uncured decreased from 3.2  
2 years (95%CI 2.2, 4.1) to 0.7 years (95%CI 0, 1.5) over this time period. There were  
3 significant differences in the percentage cured by WCC, 87% (95%CI 84, 90) for those with  
4 lower WCC and 72% (95%CI 63, 81%) for those with higher WCC. There were no  
5 differences in the percentage cured by age or sex and no differences in the median survival  
6 time of the uncured by age, sex or white cell count (Table 2, supplementary table S2).

7

8 Table 3 shows results of the EFS models. In these models, the percentage cured defines the  
9 group of patients free from relapse or who have not died. The overall trends by risk factor  
10 are similar to the model for overall survival except that the estimates of the percentage cured  
11 are slightly lower in the EFS model. The percentage cured increased from 58% (95%CI 49,  
12 66%) in 1990-97 to 86% (95%CI 81, 91%) in 2003-2011 while the median survival of the  
13 uncured decreased slightly from 2.5 years (95%CI 2.1, 2.9) to 1.3 years (95%CI 0.2, 2.5).

14

15 Based on cytogenetic risk group, the percentage cured was 92% for patients in the good risk  
16 group (95%CI 85, 94%), 84% for intermediate risk group (95%CI 68, 83%), 71% for high risk  
17 group (95%CI 48, 85) and 78% for patients with T-cell ALL (95%CI 67, 88%) (Table 4,  
18 Supplementary figure S1).

19

20 There was a substantial reduction in the risk of relapse over time; 5-years after diagnosis the  
21 cumulative incidence of relapse fell from 35% (95%CI 28, 42%) for those diagnosed 1990-97  
22 to 9% (95%CI 6, 14%) for those diagnosed 2003-2011 (Figure 2).

23

## 24 **Discussion**

25 Utilising a 'cure' model to evaluate population-based data we have confirmed an increase in  
26 the proportion of patients diagnosed with childhood ALL who have been cured with more  
27 contemporary therapeutic approaches. However, there remained a relatively small group of  
28 patients where treatment was unsuccessful and whose survival was relatively short; the

1 median survival time of the uncured diagnosed in most recent time period was around 1  
2 year. The survival trends of patients who are not long term survivors (the uncured) have not  
3 been described before, and the interpretation of trends in the survival of the uncured is  
4 difficult. Improvements in risk stratification and minimal residual disease monitoring (Vora, et  
5 al 2013) will have led to more patients moving to the cured group, leaving the most chemo-  
6 resistant patients in the uncured group. Due to the high proportion of patients 'cured' these  
7 estimates are based on a relatively small sample size and should be interpreted with  
8 caution. Key prognostic post-relapse factors are duration of first remission, site of relapse  
9 and genetic subgroup (Irving, et al 2016). This small group of 'uncured' patients may contain  
10 a heterogeneous group in terms of molecular genetics and further investigation and  
11 examination of in this group is needed.

12

13 Additionally utilising this approach for the first time in population-based data we have been  
14 able to identify an increase in the proportion cured over time based on event-free survival.  
15 This would appear to be a consequence of a significant reduction in the risk of relapse over  
16 time. Population-based estimates of EFS for ALL patients have not previously been  
17 reported, mainly due to lack of routinely collected data on relapse. Our estimates of 5-year  
18 population-based EFS for ALL patients are similar to those reported in national clinical trials:  
19 between October 1990 and March 1997 estimated 5-year EFS was 62% compared with 63%  
20 reported in the UKALLXI study (Hann, et al 2001); between April 1997 and September 2003  
21 estimated 5-year EFS was 80%, compared to 74% for ALL97 study and 80% for ALL97/99  
22 study (Mitchell, et al 2009, Moorman, et al 2010); and between October 2003 and June 2011  
23 estimated 5-year EFS was 86% compared to 87% reported by the UKALL2003 study (Vora,  
24 et al 2013). Similarly the UKALL2003 study found the 5-year cumulative incidence of relapse  
25 of 9% (Vora, et al 2013) compared to our findings of 6% during the same time period  
26 although we did not include those aged 18-24 years in our study but they were included in  
27 UKALL2003. These findings provide evidence of the validity of our estimates and  
28 completeness of the ascertainment of relapse data for the population-based YSRCCYP and

1 the potential to use routine cancer registry data to estimate long-term relapse incidence and  
2 event-free survival.

3

4 Cytogenetic information is important not only for predicting survival but also to identify  
5 patients at increased risk of relapse and those less likely to respond to treatment after  
6 relapse (Irving, et al 2016). Cancer registries do not routinely collect this information, so this  
7 is a unique feature of this study and a major strength, although there may have been  
8 changes to cytogenetic information available over time. 5-year overall survival for those in  
9 the good risk group in patients in the ALL97/99 trial was 94%, we estimated the proportion  
10 cured in this risk group to be 91% providing valuable information on the long-term survival  
11 for this group of patients.

12

13 For patients diagnosed between 2003 and 2011, the 5-year survival estimate was very  
14 similar to the percentage of patients cured. The proportion cured for childhood ALL has been  
15 increasing since the 1970s reflecting major improvements in survival during this time (Gatta,  
16 et al 2013, Shah, et al 2008). We have shown that this increasing trend continued including  
17 patients diagnosed up to 2011, however the rate of increase may have slowed down;  
18 between 1997-2003 and 2003-2011 the proportion cured increased from 84% to 89%. This  
19 is consistent with population-based survival trends reported by clinical trial era (Stiller, et al  
20 2012, van Laar, et al 2015).

21

22 The estimates of the association between risk factors and overall survival and event-free  
23 survival were similar for the cure model and the survival model that does not assume cure  
24 (supplementary Table S3), however additional information on different aspects of survival  
25 can be obtained from the cure model by considering separately the trends for the “cured”  
26 and “uncured”. The proportion cured is a useful measure of long term survival and may be  
27 more informative for communicating prognosis to patients rather than focussing on the  
28 benchmark of 5-year survival.

1

2 Key strengths of this study are the availability of population-based clinical data including  
3 cytogenetic risk group, despite this not being available for all patients. Our data showed that  
4 the survival curves tended to flatten out after 8-10 years follow-up but there may remain  
5 some excess mortality after this, suggesting that, particularly for more recently diagnosed  
6 patients, a longer follow-up period may be needed. Other study limitations are that we could  
7 not estimate cure for all subgroups due to limited sample size. A larger sample would allow  
8 the examine trends over time by patient subgroups. This study only included patients  
9 diagnosed in one region in England, however the Yorkshire region is representative of  
10 England and Wales in terms of socio-demographics (Feltbower, et al 2004). Replication of  
11 this approach in national disease registries is needed.

12

13 Statistical cure is measured at the population level and does not provide information on  
14 individual level cure. Overall survival and even event-free survival do not measure quality of  
15 survival (Barr and Sala 2005). Childhood cancer survivors are at risk of an array of late  
16 effects of treatment including excess late mortality (Armstrong, et al 2016, Fidler, et al 2016),  
17 subsequent malignant neoplasms (Friedman, et al 2010, Olsen, et al 2009, Reulen, et al  
18 2011), as well as other morbidities which may not occur until many decades after the end of  
19 treatment (Oeffinger and Robison 2007). Available data to monitor and identify these late  
20 effects are not routinely recorded within population-based cancer registries. Nonetheless,  
21 through data linkage to routinely collected primary and secondary care records there is the  
22 potential to explore these outcomes for long-term survivors and assess 'cure' based not only  
23 on survival outcomes but also through incorporating other adverse late health effects to  
24 account for these in the definition and statistical modelling of cure (Zwaan and Sposto 2013).

25

26 In conclusion, an innovative analytical approach utilising cure models has identified a  
27 reduction in relapse risk alongside a reduced absolute duration of survival for those with ALL  
28 destined to be uncured.

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## **Ethical approval**

The Yorkshire Specialist Register of Cancer in Children and Young People has received ethical approval from the Northern and Yorkshire Multi Centre Research Ethics Committee (reference number – MREC/00/3/001) and approval from the Health Research Authority Confidentiality Advisory Group (reference number – CAG 1-07(b)/2014) which permits the processing of identifiable cancer registration data without the need for informed patient consent.

## **Author contribution**

LS, AG and RGF designed the research study. LS analysed the data and drafted the manuscript. LS, AG, SK, DG, LC, AVM and RGF interpreted the results and critically reviewed the manuscript. All authors approved the final version of this paper.

## **Conflict of Interest**

The authors declare no competing interests

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1 **Tables and figures**

2 **Table 1:** Characteristics of ALL patients in Yorkshire, 1990-2011

3

4 **Table 2:** 5-year relative survival, excess mortality rate ratios, percentage cured and median  
5 survival time of uncured (including 95% confidence intervals (CI)) based on overall survival  
6 for ALL patients

7

8 **Table 3:** 5-year event-free survival, excess mortality rate ratios, percentage cured and  
9 median survival time of uncured (including 95% confidence intervals (CI)) based on relapse  
10 free survival for ALL patients

11

12 **Table 4:** Excess mortality rate ratios, percentage cured and median survival time of uncured  
13 (including 95% confidence intervals (CI)) by cytogenetic risk group for overall survival and  
14 event-free survival for ALL patients

15

16 **Figure 1:** Overall survival and event-free survival by time period, for ALL patients in  
17 Yorkshire, 1990-2011, aged 1-17 years

18

19 **Figure 2:** Cumulative incidence of relapse by diagnostic period, ALL patients in Yorkshire,  
20 1990-2011, aged 1-17 years

21

22 **Supporting Information**

23 **Supplementary table S1:** Comparison patient characteristics for those linked and not linked  
24 to cytogenetic risk group data, n(%)

25 **Supplementary table S2:** Adjusted differences in the percentage cured and median survival  
26 time of uncured (including 95% confidence intervals (CI)) based on overall survival and  
27 event free survival for ALL patients

28

- 1 **Supplementary table S3:** Unadjusted and adjusted survival model results (EMRR (%CI))
- 2 without cure assumption
- 3 **Supplementary figure S1:** Overall survival by cytogenetic risk group, for ALL patients in
- 4 Yorkshire, 1990-2011, aged 1-17 years