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Survival from childhood acute lymphoblastic leukaemia: the impact of social inequality in the United Kingdom

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ABSTRACT

Background: Survival from childhood acute lymphoblastic leukaemia (ALL) has continued to improve in economically-developed regions of the world, but 20% of patients still die within 5-years of diagnosis. Treatment is prolonged and complex; and as survival rates plateau, factors relating to socio-economic status and/or treatment adherence are increasingly scrutinised as potentially important determinants of outcome.

Methods: Predicated on the frame-work of the United Kingdom (UK) NHS, the relationship between socio-demographic factors and ALL survival is examined here using data from a large follow-up study conducted in the 1990s. One thousand five hundred and fifty nine children (0–14 years) diagnosed in England, Scotland &Wales during the era of the national UKALL XI randomized-controlled trial (RCT) were followed-up for an average of 15·9 years (20,826.3 person-years). Area-based deprivation scores and father's occupational social class at the time of the child's birth were used as markers of socio-economic status. Information on deaths was obtained from the NHS Information Centre for Health and Social Care. All children were included in the analyses, irrespective of RCT enrolment or participation in the founding epidemiological study (www.UKCCS.org).Survival effects were assessed using proportional hazards regressions models.

Results: Survival varied with both area-based deprivation at diagnosis (hazard ratio (HR) 1.29; 95% confidence interval (CI) 1.05–1.57) and fathers occupational social class at birth (HR 1.12; 95% CI 0.97–1.29); the divergence beginning 6–9 months after diagnosis, and widening thereafter during home-administered therapy. The findings became more marked when analyses were restricted to those enrolled in UKALL XI ($n = 1341$). As expected, survival differences were also observed with sex, and age at diagnosis.

Conclusion: The existence of significant social disparities in ALL survival, which are not due to treatment accessibility, is of major clinical importance. Trends should be monitored and further research into potentially modifiable risk factors conducted.

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1. Introduction

Five-year survival rates for acute lymphoblastic leukaemia (ALL) diagnosed in childhood have improved dramatically in recent decades, exceeding 80% in economically developed regions of the world.[1–5] Nonetheless, despite continued therapeutic refinements and scientific advances in disease characterisation and diagnosis, one-fifth of all children diagnosed fail to achieve this milestone. In addition to treatment regimen, it is well recognised that patient characteristics such as age and sex, as well as white cell count at presentation and disease subtype are important predictors of outcome.[1,2] Furthermore, there is increasing evidence that factors related to socio-economic status may have important roles to play; with children from less advantaged areas/families often having poorer survival.[6–14]

Here we investigate the relationship between socio-demographic characteristics and long-term survival using data from a large population-based study of childhood cancer that was undertaken in the United Kingdom (UK) in the 1990s. The UK Childhood Cancer Study (UKCCS) was predicated on the framework of the National Health Service (NHS)[15]; and all children diagnosed with cancer in England, Scotland or Wales were included, regardless of their participation in clinical trials.[16,17]

2. Methods

Comprehensive details about the conduct of the UKCCS and ethical approvals are described elsewhere (www.ukccs.org).[15,16] In brief, for the purposes of study management, the country was divided into 10 administrative areas, each the responsibility of a single epidemiological centre which operated for a specific period of time within the 1991–1996 overarching time-window. To ensure ascertainment completeness, proactive notification systems were established in all hospitals treating children (0–14 years) with cancer throughout England, Scotland and Wales; with subsequent cancer registry and clinical trial cross-checks confirming the comprehensive nature of UKCCS data capture. Children born outside of the UK were ineligible for the study. Initial study ethical approval was obtained individually from all local ethics committees in Great Britain. Updated ethical approval for the study was obtained in 2005 from the Northern and Yorkshire Multi-Centre Research Ethics Committee.

Area-based deprivation scores were derived using standard methods; full details of which have been previously published.[16] In summary, categories were derived by dividing the continuous deprivation score for national 1991 census enumeration areas into five equally-sized groups, with group one representing the most affluent and group five the least. Postcodes were used to allocate deprivation scores at both diagnosis and birth (mother's address taken from the child's birth certificate). Individual measures of social class were also assigned using father's employment status and occupation as stated at birth certification.[16]

In total 4433 case children were registered in the UKCCS, of which 1581 (35·7%) had ALL. Over 90% of children diagnosed with ALL were enrolled in a phase III randomized controlled trial (RCT), the timing of the study coinciding with UKALL XI which recruited children aged 1–15 years diagnosed with ALL between 1990 and 1997.[18] Within the UKCCS, information on subsequent deaths is routinely obtained from the National Health Service Information Centre for Health and Social Care (www.ic.nhs.uk).[17]

The analyses presented here include 1559 (98.6%) children diagnosed with ALL of which 90% were B-lineage (pre-cursor B-cell and pro-B cell) with the remainder being T-lineage. Children were followed for an average of 15.9 years (interquartile range (IQR): 10.7–17.5 years), yielding 20,826.3 person-years up to March 2011 (Table 1). Of the 22 children with ALL who were not included, 8 (0.5%) were un-traced within the NHS registration system and 14 (0.9%) did not have a valid address recorded. A total of 18 cases (1.2%) were lost to follow-up accounting for 262.2 person-years (1.2% of total).

Survival curves within each deprivation category were initially estimated using the Kaplan–Meier method.[19] The effects of deprivation on survival were assessed using proportional hazards regression models adjusted for sex and age at diagnosis.[19–21] Age at diagnosis was considered either as a continuous variable or as a four-level categorical variable. Deprivation score was modelled in three ways; using the calculated score (range: 5.99–6.96), the nationally-defined quintiles and as a binary variable comparing more deprived (the 4th and 5th quintiles) with less deprived (the 1st, 2nd and 3rd quintiles). Father's social class was modelled as either three categories; classes I and II (professional/managerial), class III (skilled manual/non-manual) or classes IV and V (semi-skilled/unskilled); or as a linear effect. We also investigated the validity of the proportional hazards assumption and the functional forms of the continuous variables (where applicable) for the various effects.[19–21] Quoted hazard ratios were estimated from a regression model including sex, a penalised spline fit[20] of the age at diagnosis, and the deprivation or social class variable being assessed.[21]

3. Results

The numbers of diagnoses and deaths, together with data on the follow-up period, are distributed by age and sex in Table 1. Of the 1559 cases, 56% were boys and around two-thirds were diagnosed before the age of 6 years (median 4.4 years, interquartile range 2.9–7.6 years). Over the follow-up period, 404 (26%) children died; a larger proportion of boys than girls (28% versus 23%). The gender divergence shown in Fig. 1 (hazard ratio$_{M:F}$ = 1.22 times higher death rate, 95% confidence interval (CI) 1.00–1.50), emerging three years post diagnosis. The relationship between survival and age at diagnosis was statistically significant and non-linear ($p < 0.001$); the greatest losses occurring in those diagnosed before their first birthday (62%) or after their 10th (41%), and the least in those diagnosed between 1–5 years (20%). In contrast to sex, however, the differences with age are apparent from the time of diagnosis onwards (Fig. 2).

Over the follow-up period fewer deaths occurred in more affluent areas, the proportions ranging from 23% in the least deprived areas through to 30% in the most deprived (Table 1); the linear hazard ratio being 1.05 (1.01–1.09) per unit increase

Table 1 – Characteristics of acute lymphoblastic leukaemia (ALL) diagnoses and deaths: United Kingdom Childhood Cancer Study.

	Diagnoses	Deaths (% of diagnoses)	Years of follow-up		
			Median (inter-quartile range)		Person-years
Total	1559	404 (25.9)	15.9	(10.7–17.5)	20,826.3
Sex					
Boys	874	246 (28.2)	15.8	(7.7–17.4)	11,444.2
Girls	685	158 (23.1)	16.1	(14.4–17.6)	9382.1
Age at diagnosis (years)					
<1	58	36 (62.1)	3.2	(1.0–16.6)	452.0
1–5	964	193 (20.0)	16.1	(14.6–17.6)	13,697.7
6–9	291	75 (25.8)	16.0	(11.2–17.4)	3895.2
10–14	246	100 (40.6)	15.4	(3.3–17.1)	2781.4
Deprivation at diagnosis[a]					
1 affluent	306	71 (23.2)	16.2	(14.3–17.4)	4189.7
2	340	83 (24.4)	16.1	(14.2–17.6)	4627.2
3	300	71 (23.7)	15.8	(14.3–17.5)	4131.4
4	318	91 (28.6)	15.8	(5.6–17.4)	4057.4
5 deprived	295	88 (29.8)	15.7	(6.1–17.7)	3820.6
Social class at birth[b]					
I/II: professional/managerial	487	114 (23.4)	16.1	(14.4–17.6)	6675.0
III: skilled manual/non-manual	609	158 (25.9)	15.8	(10.7–17.4)	8127.2
IV/V: semi-skilled/unskilled	319	95 (29.8)	15.7	(5.7–17.5)	4082.1
Other or missing	144	37 (25.7)	16.1	(12.1–17.5)	1942.0

[a] An area-based measure. Quintiles based on the national distribution of areas by deprivation.

[b] An individual-based measure. Determined from the occupation of the father recorded in the birth certificate of the child. Other father occupations include the armed forces (23), student (3) and a job that could not be coded (16). Missing occupation includes children for whom a birth certificate could not be traced (18), no father was registered (72), the social class was based on the occupation of the mother (7) or the father was unemployed (5).

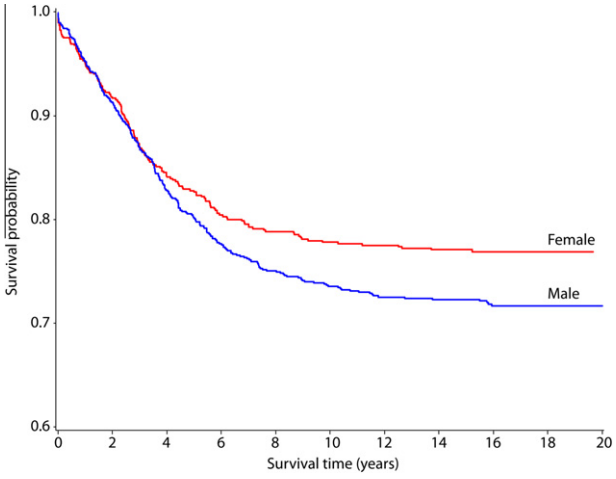

Fig. 1 – Kaplan–Meier survival estimates of children with ALL by sex. Log-rank test of heterogeneity: $\chi^2_{1df} = 4.49$, $p = 0.034$.

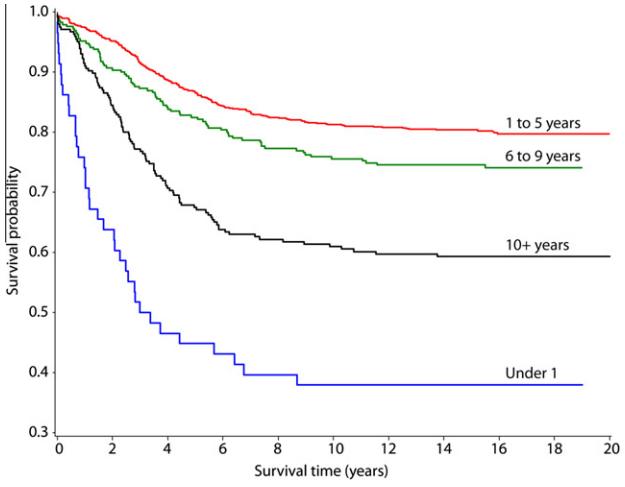

Fig. 2 – Kaplan–Meier survival estimates of children with ALL by age at diagnosis. Log-rank test of heterogeneity: $\chi^2_{3df} = 122.14$, $p < 0.0001$.

in deprivation. Overall, those in quintiles 4 and 5 were at a greater risk of dying compared to those in quintiles 1–3 (1.29, 1.05–1.57), with 10-year survival estimates differing by approximately 5% (Fig. 3a). A consistent pattern was observed when father's occupation as recorded at birth certification was used to assign individual social-class (linear effect of social class: 1.12, 0.97–1.29), the absolute 10-year difference between the lowest and highest groups being 8% (Fig. 3b). Comparable results were obtained when deprivation scores were calculated using address at birth (data not shown).

1341 (86%) children were enrolled in the national MRC trial, which recruited patients diagnosed between 1 and 15 years. As can be seen from Figs. 4a (hazard ratio$_{1–3:4–5}$1.31, 1.05–1.64) and 4b (linear effect of social class:1.16, 0.99–1.36), restricting the analysis to UKALL XI participants produced

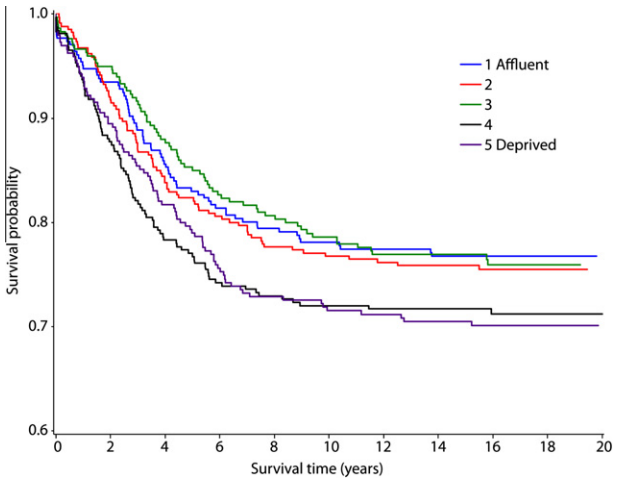

Fig. 3a – Kaplan–Meier survival estimates of children with ALL by area-based deprivation quintile at diagnosis.

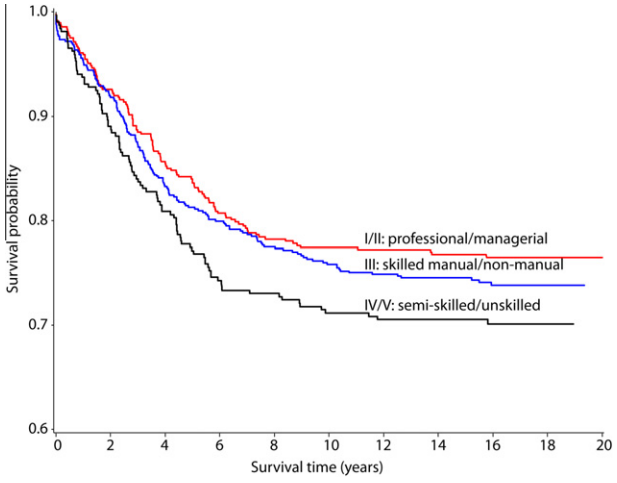

Fig. 3b – Kaplan–Meier survival estimates of children with ALL by individual measures of social class determined using father's employment status and occupation.

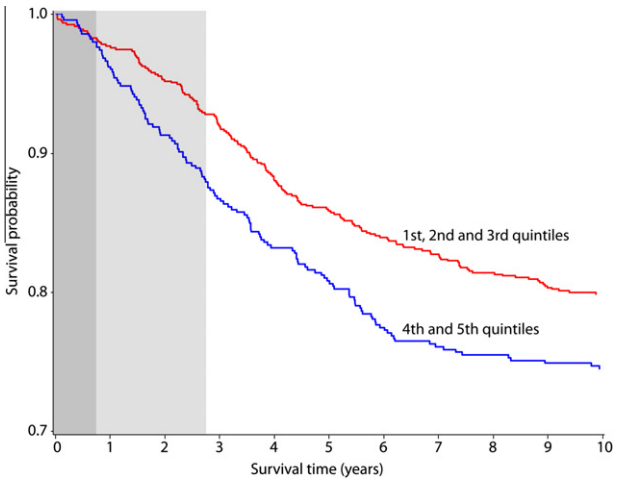

Fig. 4a – Kaplan–Meier survival estimates of children with ALL recruited to UKALL XI stratified by high (quintiles 4 & 5) and low (quintiles 1, 2 & 3) deprivation score. Shaded areas indicate hospital (dark grey) and home (light grey) administered phases of therapy.

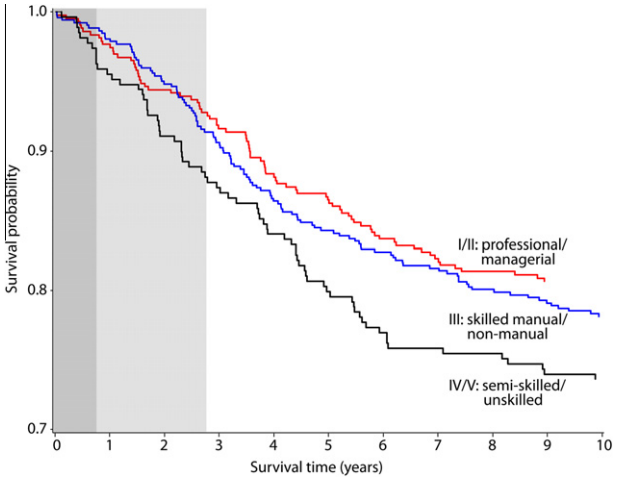

Fig. 4b – Kaplan–Meier survival estimates of children diagnosed with ALL recruited to UKALL XI stratified by social class determined using father's employment status and occupation recorded at birth cetification. Shaded areas indicate hospital (dark grey) and home (light grey) administered phases of therapy.

similar results – the divergence beginning around 6–9 months after diagnosis and widening thereafter. This broadly coincides with the shift in therapy administration from the hospital to the home environment; and the typical durations of these are also marked on the Figures.

4. Discussion

We have examined the effect of age, sex and socio-demographics on long term survival in more than 1500 cases of acute lymphoblastic leukaemia (ALL) diagnosed in the early 1990s. We used area-based deprivation and occupational information to derive socio-economic indicators; both revealing marked social inequalities in survival. In addition, we also observed that whilst sex-differences were clearly apparent, they only became manifest after treatment had finished.

An acknowledged strength of the population-based UKCCS is that it included all cases of ALL diagnosed within specified geographic areas and time-periods, irrespective of participation in clinical trials or the parent case-control study.[16] In addition, the fact that the study was predicated on the UK National Health Service is a further asset; all children had access to the same treatment and care, irrespective of their social circumstances; and the outcomes of all children were automatically tracked through routine systems.[17]

Our results with respect to age at diagnosis and sex are consistent with those described by others.[3,22] We have also

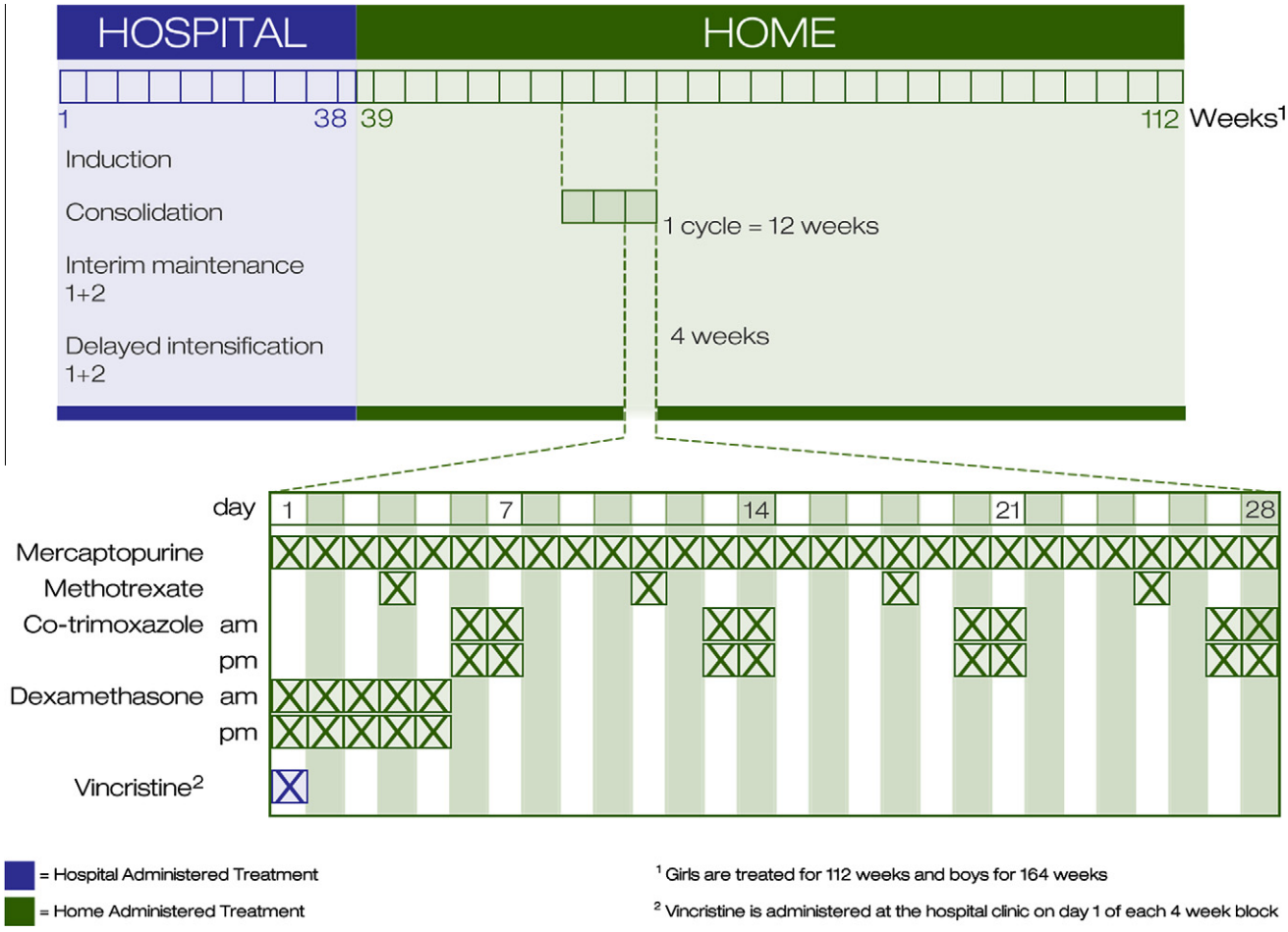

Fig. 5 – Treatment delivery protocol for acute lymphoblastic leukaemia based on the MRC UKALL 2003 trial.

demonstrated that although girls were less likely to die than boys, survival estimates were comparable until 3-years after diagnosis, at which point they began to diverge. In this regard, it is important to note that during the UKCCS era boys and girls with ALL were treated identically, both with respect to the intensity and to the length of treatment. During the last 10 years, however, UK treatment protocols have evolved, with boys having an additional 12 months of maintenance therapy.[23] Nevertheless, more recent data suggest that sex differences may still be present, even in current regimens.[24,25]

Our key finding that socio-economic factors impact on ALL survival agrees with the accumulating evidence in this area.[6–14,26,27] Hitherto, however, this issue has been more extensively addressed in less economically developed regions of the world,[8,11–14] where associations between outcome and SES have been suggested to be attributable to a range of factors including malnourishment[14,28] and treatment abandonment.[29] Findings from more economically developed countries have generally been less convincing, with only weak trends observed.[6,26,27].

In the UK scientific interest has tended to focus more firmly on the potential effects of disease biology and treatment trials[23] with information on socio-demographic factors coming from smaller studies[30,31] or earlier time periods.[32] Our analyses show not only that socio-economic factors are important, but also that the divergence becomes more striking when treatment management moves predominantly from hospital to home. Importantly, the effect is clearly evident not only among the general UKCCS patient population, but also among 85% of children entered into UKALL XI; hence confirming that the association is not due to differential treatment across social groups.

Therapy for ALL, in contrast to that for other childhood malignancies, is prolonged with current protocols now lasting up to 3 years. The complexity of the regimen is illustrated in Fig. 5, which shows the present treatment pathway in the UK (UKALL 2003), the basic structure and timings of which are similar to those of UKALL XI which was on-going during the UKCCS. In the first 8–9 months, the majority of treatment (involving combination chemotherapy induction, consolidation and central nervous system directed treatment, followed by intensive blocks of combination chemotherapy) is administered in hospital with the onus being on clinical staff to monitor and manage all aspects of care. The highly demanding home-based therapy is delivered in 12 week cycles, and comprises daily drug administrations and monthly outpatient appointments. The frequency and timing of prescribed doses vary by drug and within the cycle; for example, mercaptopurine should be given daily 1 h after evening meals, methotrexate weekly, dexamethasone twice daily after food for the first 5 days of each cycle, and co-trimoxazole morning and evening but only on two consecutive days each

week. In addition to managing such complex treatment protocols, parents also need to be vigilant for any change in health that may need urgent hospital attendance.

Adherence to such a regimen whist trying to maintain some semblance of normal family life is clearly demanding and compliance with the prescribed treatment plan for ALL has been identified as potentially problematic, although how this relates to socio-economic status has not been investigated. However, socio-economic differences in adherence to demanding treatment protocols have been demonstrated for adolescents,[33,34] as well as for children with other chronic conditions where prolonged treatment is required, such as cystic fibrosis and juvenile diabetes[35,36].

With respect to ALL initiation, in agreement with others,[37] no associations between markers of socio-economic status and disease risk were found in the UKCCS.[16] However, of major clinical importance is the observation that whilst the development of the disease itself may not be related to socio-economic factors, mortality patently is. This social disparity is clearly not due to treatment accessibility, as is evidenced by the unequivocal findings within the RCT dataset. We conclude that systems should be put in place to monitor future socio-economic trends, and that research into investigating potentially modifiable risk factors, such as treatment adherence, should be incorporated into future RCTs.

Authors and contributors

All authors contributed to the conception and design, critically reviewed the manuscript and approved the final version. T.L. and E.R. drafted the reports, W.T.J., J.S., A.S. and S.C. conducted the analyses, and P.A. and S.E.K. provided clinical expertise.

Role of the funding source

The funding source (Leukaemia & Lymphoma Research) did not have any role in the design of the study, the collection, analysis and interpretation of the data, the writing of the manuscript, or the decision to publish. The corresponding author had full access to all data and the final responsibility for the decision to submit the manuscript for publication.

Conflict of interest statement

None declared.

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