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Secondhand smoke: A new and modifiable prognostic factor in childhood acute lymphoblastic leukemias.

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ABSTRACT

Background: The 5-year overall survival (OS) in childhood acute lymphoblastic leukemia (ALL) has reached 90% in high-income countries, levels that can no be longer overcome with strategies based on intensification of treatment. Other approaches in the search for new and modifiable prognostic factors are necessary to continue to improve these rates. The importance of environmental factors in the etiopathogenesis of childhood ALL has been regaining interest but its role in the prognosis and survival of this disease is not well explored. We aim to investigate the association between secondhand smoke (SHS) and survival in children diagnosed with ALL.

Methods: We analyzed survival rates in 146 patients under the age of 15 years diagnosed with ALL between January 1998 and May 2016 in the Region of Murcia, Spain. Evaluation of parental SHS and other known prognostic factors (sex, age, white blood cell count at diagnosis, cytogenetics, NCI/Rome Criteria, early response to therapy, and relapse) were assessed for impact on OS, event-free survival (EFS), cumulative incidence of relapse (CIR), and treatment-related mortality (CITRM) using Kaplan-Meier analysis, Cox regression, and Fine-Gray model.

Results: The mean follow-up time was 105.3 months (± 66.5). Prenatal exposure to SHS due to parental smoking was highly prevalent. Of the mothers, 44.4% and 55.5% of the fathers smoked at some point during pregnancy. After the child's diagnosis of ALL 39.7% of mothers and 45.9% of fathers reported smoking. The Cox proportional hazards model showed that maternal smoking during pregnancy and after diagnosis (HR = 4.396, 95% CI: 1.173-16.474, $p = 0.028$); and relapse (HR = 7.919; 95% CI: 2.683-21.868; $p < 0.001$) are independent prognostic factors in determining survival. The Fine-Gray model showed that maternal smoking during pregnancy and after diagnosis (HR = 14.525, 95% CI: 4.228-49.90, $p < 0.001$) is an independent prognostic factor in CITRM.

Conclusions: Persistent SHS worsens OS and TRM in children with ALL. This negative impact contributes to a different prognosis and may possibly provide an exceptional insight into new therapeutic approaches, including environmental aspects such as prevention and smoking cessation to improve survival outcomes.

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1. Introduction

Acute leukemia (AL) is the most frequent malignant disease in children younger than 15 years old, and 80% of AL cases are classified as acute lymphoblastic leukemia (ALL) (Imbach, 2014). Worldwide age-standardized incidence rate is 46.4 cases/10^6 children and it is higher in high-income countries (Steliarova-Foucher et al., 2017). The crude incidence rate of AL/ALL in Spain and in the Region of Murcia are 47.4/37.1 and 42.7/31.9 per 10^6 children, respectively (Cárceles-Álvarez et al., 2017; RNTI-SEHOP, 2017). It is estimated that the incidence of ALL is increasing globally (Bonaventure et al., 2017; Steliarova-Foucher et al., 2017; Ward et al., 2014).

Only a few causes of childhood leukemia have been established so far, mainly certain genetic syndromes and high doses of ionizing radiation (Schüz and Erdmann, 2016). The existence of distinct incidence patterns by sex, age, and geography suggest a potential role of the environment in its etiology and is a topic that is garnering interest (Whitehead et al., 2016). Due to the young age at diagnosis and evidence of chromosomal damage before birth in many of the affected children, prenatal exposures are of high interest (Schüz and Erdmann, 2016). Previous studies have shown an association between childhood ALL and prenatal exposure to secondhand smoke (SHS) (Ferrís Tortajada et al., 2004; IARC, 2012; Whitehead et al., 2016), which is known to be a human carcinogen (IARC, 2012). In fact, in studies of adults diagnosed with leukemia, persistent tobacco use is associated with a significant decrease in the overall survival of AL (Chelghoum et al., 2002; Lee et al., 2012; Varadarajan et al., 2012; Warren et al., 2013).

During the last decades, survival of childhood ALL has shown a dramatic improvement in high-income countries, from < 10% during the 1960's to near 90% in recent years (Hunger and Mullighan, 2015; Ward et al., 2014). This must be attributed in part to risk-directed therapy strategies and adequate stratification of patients according to various prognostic factors (Hunger and Mullighan, 2015; Möricke et al., 2008; Teachey and Hunger, 2013).

Factors such as age, white blood cell (WBC) count at diagnosis, cytogenetic abnormalities, and early response to therapy, are currently considered for risk-group stratification (Hunger and Mullighan, 2015; Pui et al., 2008; Smith et al., 1996; Vrooman and Silverman, 2009). Moreover, risk-directed therapy allows the reduction of treatment intensity for certain groups, contributing to the reduction of long-term adverse events (Hunger and Mullighan, 2015; Möricke et al., 2008; Pui et al., 2008). However, the trend in this progressive improvement in survival rates is showing a tendency to slow down (Bonaventure et al., 2017; Madanat-Harjuoja et al., 2014), and further intensification of chemotherapy is unlikely to cure additional patients.

This deceleration in increasing survival rates in combination with the limited progress in etiological studies suggests the need to explore other unknown factors for the prognosis of ALL. Current research focuses on the biological features of leukemia itself as well as patient pharmacogenetics (Teachey and Hunger, 2013; Vrooman and Silverman, 2009), with exposures to environmental factors being little explored. We aim to investigate the association between SHS and survival in children diagnosed with ALL in the Spanish Region of Murcia.

2. Methods

2.1. Study design

This is a survival study conducted in the MACAPEMUR cohort (Environment and Childhood Cancer in the Region of Murcia). The cohort consists of children who were < 15 years old at the time of diagnosis with ALL between January 1, 1998, and May 31, 2016, in the Region of Murcia (Spain) and who were followed up until May 31, 2018.

MACAPEMUR is a project that compiles the Pediatric Environmental History (PEHis) of newly diagnosed cancer patients under the age of 15 within the Region of Murcia since 1998 (Cárceles-Álvarez et al., 2017; Ferrís Tortajada et al., 2004; Ortega-García et al., 2011). MACAPEMUR is part of the ENSUCHICA (Environment, Survival and Childhood Cancer) network. This is a multidisciplinary network whose aim is to improve the environmental health and the survivorship of childhood cancer patients through structured knowledge exchange, capacity building, and international collaboration (Ortega-García et al., 2019). The PEHis questionnaire is an integrative tool that allows for the registration of risk factors, treatment characteristics, late effects and quality of life related to childhood cancer. Its purpose is to help propose etiological hypotheses and to help create a personalized care plan to build a high-quality long-term follow-up (Cárceles-Álvarez et al., 2017; Ferrís Tortajada et al., 2004; Ortega-García et al., 2012). Once the diagnosis is made, PEHis is carried out in face-to-face interviews with both parents by a doctor trained in long-term follow-up of childhood cancer, environmental health and risk communication.

The single-province character of the Region of Murcia and the centralized care reference units of Pediatric Oncohematolgy and the Pediatric Environmental Health Speciality Unit (PEHSU) at Clinical University Hospital “Virgen de la Arrixaca” facilitated the access to medical records. The hospital registers almost 100% of the children diagnosed with cancer in the Region. The classification of the cases is done by corroborating the clinical-pathological diagnosis with the International Classification of Diseases for Oncology (ICD-O-3) (Fritz et al., 2000) and the International Classification of Childhood Cancer (ICCC-3) (Steliarova-Foucher et al., 2005) within 0–2 months after diagnosis. Over 99% of the cases are morphologically verified through pathology review. Annually, a physician performs an additional check of all cases to avoid misclassification and/or double registrations.

2.2. Study variables

Data on parental smoking habits is collected throughout critical periods of development (Ortega-García et al., 2010). For this study, the critical periods considered were: a) any time during pregnancy, and b) after diagnosis, during the treatment of the disease. A smoker was defined as any person who smokes any tobacco product daily or occasionally (at least one cigarrete a week during the critical periods defined above).

The main variable of the study was the exposure to SHS in children diagnosed with ALL as result of the consumption of parental (father and/or mother) tobacco and included intrauterine exposure and after diagnosis exposure. The remaining variables included in this study were: sex, age at diagnosis, WBC count at diagnosis, cytogenetic and genomic features, risk group stratification according to NCI/Rome criteria (Smith et al., 1996), relapse and response to treatment at day +14.

The individuals were classified into four independent categories based on whether the parents smoked (Yes) or did not smoke (No) in the two critical periods considered. A dummy variable was used in the analysis to identify each of the four possible categories (Yes-Yes; Yes-No; No-Yes; No–No).

2.3. Statistical analysis

We considered different time-to-event outcomes. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Event-free survival (EFS) was defined as the time from diagnosis until the date of relapse, subsequent malignant neoplasm or death, whichever occurs earlier. We also used a previously developed, reliable and valid treatment-related mortality (TRM) definition, described as death occurring in the absence of progressive cancer (Alexander et al., 2015). Lost to follow-up was defined as losing contact after complete curative therapy.

We used survival analysis methods to determine the effect of the

variables included in the study on time-to event outcomes. To analyze OS and EFS, the Kaplan-Meier method was used to generate survival curve and the Log-Rank test was used to examine differences between the survival distributions of each covariate. Lastly, the Cox proportional hazards model was used to explore multivariate associations. Cumulative incidence of TRM and relapse were estimated as described by Kalbfleisch-Prentice (Kalbfleisch and Prentice, 1980) and compared by Gray's method (Gray, 1988), accounting for not Treatment-Related Mortality and exitus without relapse as a competing risk respectively. Effects were described using hazard ratio with a confidence interval of 95%, including in the multivariate models all of the variables explored. Statistical significance was established for a p-value of < 0.05.

Statistical analysis was performed using the R statistical software version 3.5.0 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org) with the R package "cmprsk" and IBM SPSS Statistics for Mac OS X, version 24.0. Armonk, NY: IBM Corp.

3. Results

3.1. Descriptive analysis

A total of 146 children with ALL were enrolled in our study, with an age at diagnosis between 1 month and 13.4 years, with an average age of 5.0 years. There was total adherence and compliance to the treatment, with no abandonment of treatment in any case. The average time of follow up was 105.3 months (Standard Deviation (SD) 66.2). Four patients (2.74%) were lost to follow-up after a follow-up of 3, 4, 7 and 12 years, respectively.

Table 1 shows parental smoking of the children with ALL. During pregnancy, 44.4% (n = 63) of mothers and 55.5% (n = 81) of fathers smoked. After diagnosis was made, 39.7% (n = 58) of mothers and 45.9% (n = 67) of fathers reported smoking. 37.2% (n = 54) of mothers and 43.4% (n = 62) of fathers smoked during both of the critical periods studied (Yes-Yes).

Table 2 shows the distribution of the variables studied, as well as the rates of OS, EFS, CITRM, and CIR at five years according to the clinical-biological characteristics and the SHS data of the population. When looking at distribution by sex there was a slight predominance of males (52.7%, n = 77). In regards to the classic prognostic factors, it is worth noting that 15.8% (n = 23) are of an unfavorable age at diagnosis (≤ 1 or ≥ 10 years), 22.6% (n = 33) had a WBC count $\geq 50{,}000/\mu L$ at diagnosis and 8.2% (n = 12) had unfavorable cytogenetic or chromosomal alterations: hypodiploid (DNA index < 0.81), translocation t(4; 11) or MLL rearrangements, translocation t(9; 22) or BCR/ABL rearrangement and translocation t(1; 19). 31.5% (n = 46) were classified in a high-risk group and 8.3% (n = 12) had an unfavorable response to treatment at day +14 (measured as a presence $\geq 5\%$ of blasts in bone marrow). 21 patients (14.4%) had a relapse, and 18 patients died (12.3%).

3.2. Overall survival

The five-year OS probability was 88.9% (Standard Error (SE) 0.03) for the entire study population. The following features were univariately associated with inferior OS: relapse, response to treatment at day +14 and maternal smoking status Yes-Yes. Also associated, although without reaching statistical significance was unfavorable age at diagnosis and paternal smoking status Yes-Yes. The five-year OS in children whose mothers smoked in the two periods (Fig. 1A) was 80.9% (SE 0.06), while in non-smokers was 93.4% (SE 0.03); odds ratio 3.38, 95% confidence interval 1.25 to 9.14, p-value 0.011. When the fathers smoked in both periods, the OS rate was 83.5% (SE 0.05), compared to 92.5% (SE 0.04) when they did not smoke in any period; odds ratio 2.51, 95% confidence interval 0.93 to 6.79, p-value 0.06. Children diagnosed at an unfavorable age had a five-year OS of 78.3% (SE 0.09), while those diagnosed at a favorable age had an OS of 90.8% (SE 0.03); odds ratio 2.41, 95% confidence interval 0.86 to 6.79, p-value 0.084. Children with an unfavorable response to treatment presented with a five-year OS of 65.6% (SE 0.14) while those with a favorable response had an OS of 90.8% (SE 0.03); odds ratio 3.94, 95% confidence interval 1.29 to 12.0, p-value 0.009. Lastly, the OS rate at five years in patients who had a relapse was 61.5% (SE 0.11), while in those who did not relapse was 93.5% (SE 0.02); odds ratio 8.05, 95% confidence interval 3.17 to 20.43, p-value < 0.001. In the multivariable analysis (Table 3), maternal smoking status Yes-Yes (hazard ratio 4.40, 95% confidence interval 1.17 to 16.47, p-value 0.028) and relapse (7.92, 2.67 to 23.50, p-value < 0.001) where the variables that remained statistically significantly associated with inferior OS.

3.3. Event-free survival

A total of 30 (20.5%) patients experienced an event: 21 relapses, 1 SMN and 8 deaths. Overall, the five-year EFS was 80.2% (SE 0.03). In the univariate analysis (Table 2), response to treatment and unfavorable age at diagnosis was associated with lower EFS. Children with an unfavorable response at day +14 had a five-year EFS of 65.6% (SE 0.14) compared to 90.8% (SE 0.03) in those who had a favorable response; odds ratio 4.62, 95% confidence interval 1.97 to 10.84, p-value < 0.001. Those of unfavorable age had a five-year EFS of 64.2% (SE 0.10), compared to 83.2% (SE 0.03) of those within a favorable age; odds ratio 2.36, 95% confidence interval 1.05 to 5.23, p-value 0.032. When analyzing parental smoking, it is worth noting that the five-year EFS of children with maternal smoking status Yes-Yes was 73.3% (SE 0.06) compared to 82.3% (SE 0.05) of the No–No; odds ratio 1.76, 95% confidence interval 0.85 to 3.66, p-value 0.121 (Fig. 1B). In the multivariable analysis (Table 3), only unfavorable response to treatment remained statistically significant associated with low EFS (hazard ratio 4.63, 95% confidence interval 1.86 to 11.53, p-value 0.001).

3.4. Cumulative incidence of treatment-related mortality

TRM occurred in 10 out of 18 deaths (55.5%). Using the classification provided by Alexander et al. (2015) seven exitus were from infectious causes, two of the gastrointestinal system (acute hepatic dysfunction and hepatic sinusoidal obstruction syndrome) and one immunomediated (secondary to graft-versus-host disease) (Table 4). The CITRM in the whole group was 6.25% (SE 0.02) at five years. There was a statistically significant difference in the five-year CITRM in patients whose mother's smoking status was Yes-Yes (odds ratio 16.7, 95% confidence interval 7.96 to 35.1, p-value < 0.001) (Table 2; Fig. 1C)

Table 1
Parental tobacco history.

	Pregnancy		After diagnosis		Yes-Yes	Yes-No	No-Yes	No–No
	n (%)	cig/w	n (%)	cig/w	n (%)	n (%)	n (%)	n (%)
Maternal	63 (44.4)	88.5 (74.6–102.4)	58 (39.7)	89.0 (74.7–103.3)	54 (37.2)	9 (6.3)	4 (2.8)	76 (53.1)
Paternal	81 (55.5)	117.0 (100.6–133.3)	67 (45.9)	118.0 (99.9–136.1)	62 (43.4)	23 (16.1)	5 (3.5)	53 (37.1)

Cig/w: cigarettes per week. Yes-Yes: Smokers during pregnancy and after diagnosis. Yes-No: Smokers during pregnancy not after diagnosis. No-Yes: Non-smokers during pregnancy, smokers after diagnosis. No–No: Non-smokers at any time.

Table 2
Overall survival (OS), Event Free Survival (EFS), Cumulative Incidence of Treatment-Related Mortality (CITRM), and Cumulative Incidence of Relapse (CIR) of patients according to selected characteristics.

Variables	N (%)	5 – year OS		5 – year EFS		5 – year CITRM		5 – year CIR	
		% (SE)	p - value	% (SE)	p - value	% (SE)	p - value	% (SE)	p - value
Sex									
Male	77 (52.7)	88.0 (0.04)	0.815	81.4 (0.05)	0.482	7.24 (0.03)	0.401	12.5 (0.04)	0.899
Female	69 (47.3)	89.8 (0.04)		79.0 (0.05)		5.41 (0.02)		14.7 (0.04)	
Age at diagnosis									
> 1 - < 10 years	123 (84.2)	90.8 (0.03)	0.084	83.2 (0.03)	0.032*	4.95 (0.02)	0.175	11.8 (0.03)	0.167
≤ 1 or ≥ 10 years	23 (15.8)	78.3 (0.09)		64.2 (0.10)		13.0 (0.07)		25.0 (0.09)	
WBC count at diagnosis									
< 50,000/μL	113 (77.4)	89.1 (0.03)	0.567	81.4 (0.04)	0.261	5.42 (0.02)	0.547	12.9 (0.03)	0.384
≥ 50,000/μL	33 (22.6)	87.9 (0.06)		75.8 (0.08)		9.20 (0.05)		16.1 (0.07)	
Unfavorable cytogenetic									
Yes	12 (8.2)	83.3 (0.11)	0.579	50.0 (0.17)	0.054	6.05 (0.02)	0.825	12.6 (0.03)	0.258
No	134 (91.8)	89.4 (0.03)		82.5 (0.03)		9.09 (0.09)		25.9 (0.14)	
NCI/Rome risk group									
Standard	100 (68.5)	89.7 (0.03)	0.435	82.3 (0.04)	0.232	5.11 (0.02)	0.533	12.5 (0.03)	0.392
High	46 (31.5)	87.0 (0.05)		75.8 (0.06)		8.74 (0.04)		16.3 (0.06)	
Day +14 BM blasts (n = 145)									
< 5%	133 (91.7)	90.8 (0.03)	0.009*	83.8 (0.03)	< 0.001*	6.06 (0.02)	0.735	10.9 (0.03)	0.002*
≥5%	12 (8.3)	65.6 (0.14)		37.5 (0.15)		8.33 (0.08)		50.0 (0.17)	
Relapse									
Yes	21 (14.4)	61.5 (0.11)	< 0.001*	NA	NA	12.9 (0.09)	0.124	NA	NA
No	125 (85.6)	93.5 (0.02)				5.62 (0.02)			
Maternal smoking status (n = 143)									
Yes-Yes	54 (37.8)	80.9 (0.06)	0.011*	73.3 (0.06)	0.121	15.0 (0.05)	< 0.001*	16.4 (0.05)	0.745
Yes-No	9 (6.3)	–	0.276	–	0.141	6.07 (0.02)	0.418	–	0.190
No-Yes	4 (2.8)	–	0.464	–	0.324	5.85 (0.02)	0.596	–	0.391
No–No	76 (53.1)	93.4 (0.03)	0.098	82.3 (0.05)	0.705	1.21 (0.04)	0.001*	14.7 (0.04)	0.524
Paternal smoking status (n = 143)									
Yes-Yes	62 (43.4)	83.5 (0.05)	0.060	73.4 (0.06)	0.142	9.96 (0.04)	0.055	19.1 (0.05)	0.301
Yes-No	23 (16.1)	95.7 (0.04)	0.224	91.3 (0.06)	0.311	4.34 (0.04)	0.668	4.5 (0.04)	0.349
No-Yes	5 (3.5)	–	0.401	–	0.262	–	0.552	–	0.335
No–No	53 (37.1)	92.5 (0.04)	0.523	82.0 (0.06)	0.810	1.88 (0.02)	0.097	13.4 (0.05)	0.973

SE: Standard Error. NA: Not Applicable. WBC: White Blood Cell. BM: Bone marrow. Unfavorable cytogenetic: hypodiploid (DNA index < 0.81), t(4; 11) or MLL rearrangements, t(9; 22) and t(1; 19).
Smoking status: Yes-Yes: Smokers during pregnancy and after diagnosis; Yes-No: Smokers during pregnancy not after diagnosis. No-Yes: Non-smokers during pregnancy, smokers after diagnosis. No–No: Non-smokers at any time.

and a relationship is observed, though it does not reach statistical significance with paternal smoking status Yes-Yes (4.64, 0.97 to 22.2, *p*-value 0.055). In the multivariable model, the maternal smoking status Yes-Yes remained significant (hazard ratio 14.53, 95% confidence interval 4.23-49.90, *p*-value < 0.001) (Table 3).

3.5. Cumulative incidence of relapse

Finally, the CIR for the whole group was 19.6% (SE 0.03). In the univariate analysis, only unfavorable response to treatment was associated with increased CIR (odds ratio 4.15, 95% confidence interval 1.6 to 10.8, *p*-value 0.002) and remained significant in the multivariable model (hazard ratio 3.77, 95% confidence interval 1.30 to 10.94, *p*-value 0.015) (Table 3). SHS had no impact on the CIR (Fig. 1D).

4. Discussion

Our work shows that exposure to persistent SHS and relapse are prognostic factors related to OS. Previous studies also demonstrate that relapse is a key factor in explaining OS (Chessells et al., 2003; Hunger et al., 2011; Nguyen et al., 2008), however, this is the first paper, as far as we know, that explores and finds a significant association between SHS with an adverse OS in patients with childhood ALL, increasing the CITRM. The percentage of survivors in our study exposed to SHS is alarmingly high (> 45%), compared to prevalence of SHS exposure in Spanish children in private settings which is 29.2% (Lletjós et al., 2018). An additional consideration is that Spain has one of the highest prevalences of smoking when compared to other countries of Western Europe (GBD 2015 Tobacco Collaborators, 2017).

For the other prognostic factors (sex, age, WBC count, cytogenetics, response to treatment and NCI/Rome criteria) we did not find statistically significant differences, probably due to treatments that are more intense and adjusted according these classic prognostic factors. The rate of OS, EFS and CIR observed in our sample is comparable to that of Spain and other high-income countries (Bonaventure et al., 2017; Lum et al., 2017; Vora, 2017) while the CITRM is slightly higher (6.25% vs < 5%) (Orgel and Bhojwani, 2017), likely because we included in our analysis patients after relapse.

Few peer-reviewed publications are available that investigate the association between environmental exposures and the prognosis of childhood leukemias. Most studies assess that have searched for environmental causes have focused on the association between exposure to very low frequency electromagnetic fields and the survival of infant ALL, obtaining conflicting results (Schüz et al., 2012; Svendsen et al., 2007). The relationship between socioeconomic status and survival in ALL has shown mixed results. While some studies associate a lower socio-economic status with lower survival in low- and middle-income countries, other studies in high-income countries show that this association is linked to access to healthcare (Gupta et al., 2014; Petridou et al., 2015). In our sample, although we have not been able to analyze the effect of socioeconomic status on survival, this potential relationship would be minimized since Spain has access to a universal healthcare system which supports the cost of all medical procedures. Universal and free access to healthcare also ensures proper compliance and adherence to treatments.

In recent years, there have been conducted other studies analyzing

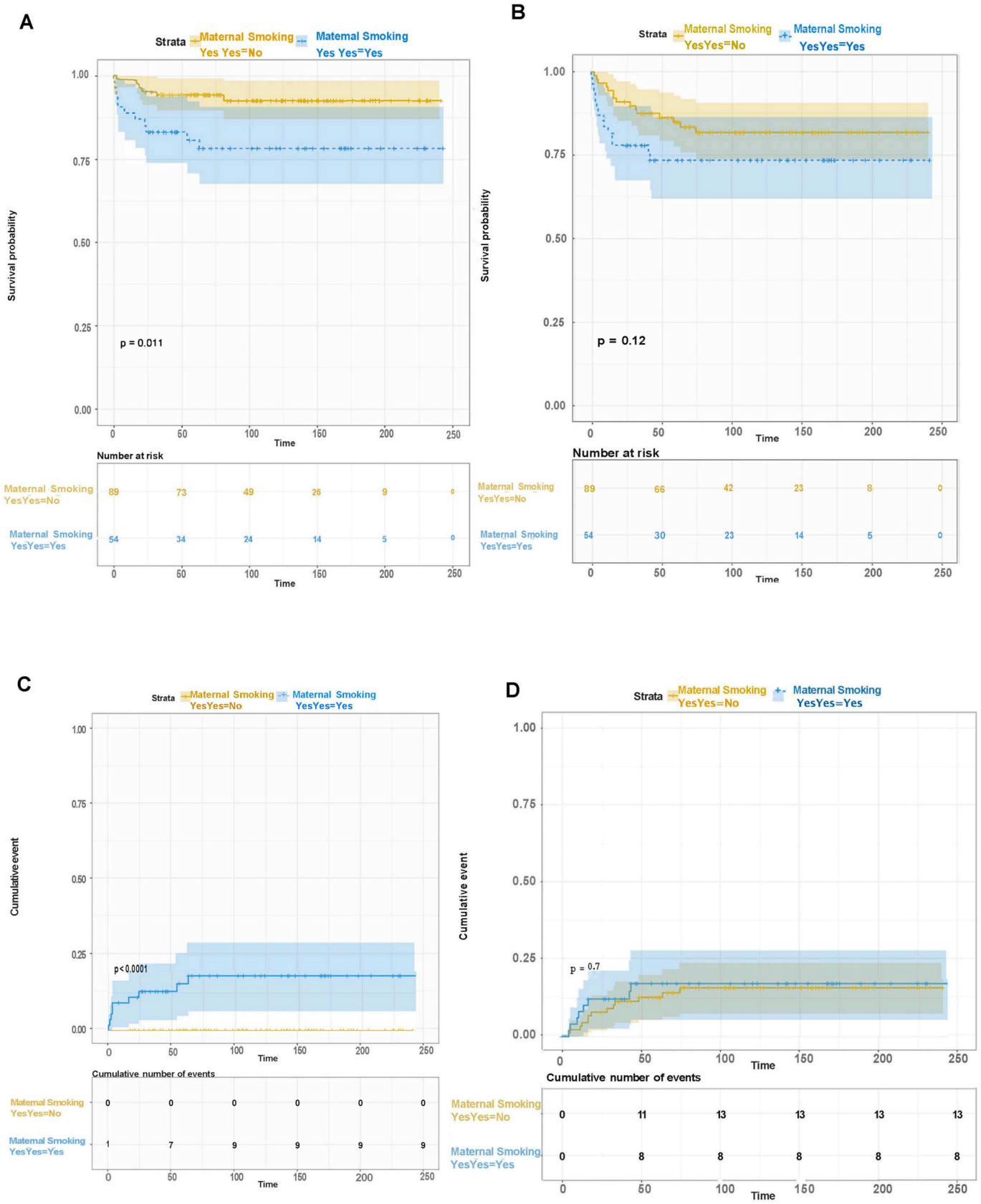

Fig. 1. Overall Survival (A), Event-Free Survival (B), Cumulative Incidence of Treatment-Related Mortality (C) and Cumulative Incidence of Relapse (D) in childhood acute lymphoblastic leukemia according to maternal smoking status Yes-Yes. *Shaded areas indicate 95% CI.*

Table 3
Multivariate analysis of prognostic factors in Overall Survival (OS) and Event-Free Survival (EFS) by the Cox proportional hazards model, and in cumulative incidence of Treatment-Related Mortality (CITRM) and relapse (CIR) by the Fine & Gray model in childhood acute lymphoblastic leukemia.

Variable	OS			EFS			CITRM			CIR		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Sex												
Male[a]	–	–	–	–	–	–	–	–	–	–	–	–
Female	0.917	0.317–2.648	0.872	0.958	0.441–2.081	0.913	0.654	0.174–2.46	0.53	1.218	0.498–2.97	0.670
Age (years)												
> 1 - < 10[a]	–	–	–	–	–	–	–	–	–	–	–	–
≤1 or ≥10	2.646	0.292–23.986	0.387	3.150	0.762–13.011	0.113	1.369	0.006–286.1	0.91	2.775	0.532–14.49	0.230
WBC at diagnosis												
< 50,000/μL[a]	–	–	–	–	–	–	–	–	–	–	–	–
≥50,000/μL	0.906	0.114–7.208	0.925	2.615	0.548–12.477	0.228	0.888	0.012–65.45	0.96	2.562	0.436–15.05	0.300
Unfavorable cytogenetic												
No[a]	–	–	–	–	–	–	–	–	–	–	–	–
Yes	1.035	0.160–6.706	0.971	2.017	0.639–6.373	0.232	1.465	0.029–73.15	0.85	1.464	0.325–6.60	0.620
NCI/Rome risk group												
Standard[a]	–	–	–	–	–	–	–	–	–	–	–	–
High	0.599	0.041–8.685	0.707	0.277	0.039–1.951	0.198	0.775	0.003–183.2	0.93	0.342	0.031–3.83	0.380
Day +14 BM blasts												
< 5%[a]	–	–	–	–	–	–	–	–	–	–	–	–
≥5%	2.790	0.721–10.791	0.137	4.630	1.860–11.525	0.001*	1.293	0.059–27.88	0.87	3.771	1.299–10.94	0.015*
Relapse												
No[a]	–	–	–	NA	NA	NA	–	–	–	NA	NA	NA
Yes	7.919	2.669–23.498	< 0.001*				3.434	0.773–15.26	0.10			
Maternal smoking status												
Yes-No; No-Yes; No–No[a]	–	–	–	–	–	–	–	–	–	–	–	–
Yes-Yes	4.396	1.173–16.474	0.028*	1.725	0.766–3.882	0.188	14.525	4.228–49.90	< 0.001*	0.946	0.400–2.24	0.900
Paternal smoking status												
Yes-No; No-Yes; No–No[a]	–	–	–	–	–	–	–	–	–	–	–	–
Yes-Yes	0.957	0.263–3.479	0.946	1.503	0.661–3.414	0.331	1.720	0.211–14.01	0.61	1.438	0.664–3.11	0.360

SE: Standard Error. HR: Hazard Ratio. CI: Confidence Interval.
WBC: White Blood Cell. BM: Bone marrow.
Unfavorable cytogenetic: hypodiploid (DNA index < 0.81), t(4; 11) or MLL rearrangements, t(9; 22) and t(1; 19).
Smoking status: Yes-Yes: Smokers during pregnancy and after diagnosis; Yes-No: Smokers during pregnancy not after diagnosis. No-Yes: Non-smokers during pregnancy, smokers after diagnosis. No–No: Non-smokers at any time.
[a] Reference. NA: Not Applicable.

parental smoking as an etiological risk factor for childhood leukemia (Ferrís Tortajada et al., 2004; IARC, 2012; Whitehead et al., 2016). Some articles have also looked at prenatal and early-life tobacco exposure (de Smith et al., 2017). However, parental tobacco smoking has not been studied in this population as a prognostic factor for ALL outcomes. There are few studies, all of them in adults, that associate the tobacco products with a higher mortality from leukemias, mainly acute myeloblastic leukemia (AML) (Chelghoum et al., 2002; Lee et al., 2012; Varadarajan et al., 2012; Warren et al., 2013).

Although we observe a trend of decreasing OS with persistent smoking (Yes-Yes) of both parents, the association with maternal tobacco consumption is the major statistically significant effect. The role

Table 4
Descriptive analysis of death causes.

Patient	Death cause[a]	Risk group stratification	Relapse	Survival (months)	Event-Free (months)	Maternal smoking status	Paternal smoking status
1	NTRM – Progression	High	Yes	8	4	Yes-Yes	Yes-Yes
2	NTRM – Progression	High	Yes	81	74	No–No	No–No
3	TRM - Infection	Standard	Yes	54	42	Yes-Yes	Yes-Yes
4	NTRM – Progression	Standard	Yes	23	10	Yes-Yes	Yes-Yes
5	TRM – Infection	Standard	No	1	1	Yes-Yes	Yes-Yes
6	TRM - Gastrointestinal	High	No	3	3	Yes-Yes	No–No
7	NTRM – Progression	Standard	Yes	19	11	No–No	No–No
8	TRM – Infection	High	No	0	0	Yes-Yes	Yes-Yes
9	TRM – Infection	Standard	No	2	2	Yes-Yes	[b]
10	TRM - Immunomediated	High	No	16	16	Yes-Yes	Yes-Yes
11	TRM – Infection	Standard	Yes	63	43	Yes-Yes	Yes-Yes
12	NTRM – Progression	High	Yes	17	12	No–No	No–No
13	NTRM – Progression	Standard	Yes	32	28	No–No	Yes-Yes
14	TRM – Infection	Standard	No	3	3	Yes-Yes	Yes-Yes
15	NTRM – Progression	Standard	Yes	21	16	No–No	No–No
16	NTRM – Progression	Standard	No	2	2	No–No	Yes-Yes
17	TRM - Infection	Standard	Yes	24	13	Yes-Yes	Yes-Yes
18	TRM - Gastrointestinal	High	No	1	1	[b]	[b]

TRM: Treatment-related mortality. NTRM: Not treatment-related mortality.
[a] According to Alexander et al. (2015).
[b] Unknown smoking status.

of the mother as the main caregiver when a child is diagnosed with cancer is known (Wiener et al., 2017; Willard et al., 2017), so it is understandable that the main source of exposure to SHS both in pregnancy and in the long periods of treatment of ALL, comes from the mother. Additionally, OS does not change with the amount of cigarettes smoked by parents (Table S1, supplementary material), which could indicate an individual susceptibility to the effects of tobacco, regardless of parental consumption.

The observed effects on the survival due to persistent tobacco exposure during pregnancy and after diagnosis could be explained in multiple ways. Firstly, previous studies have associated prenatal exposure to tobacco smoke to the presence of leukemogenic cytogenetic alterations with worse prognosis (such as the MLL rearrangement) in offspring (Andrade et al., 2014; de la Chica et al., 2011; de Smith et al., 2017) and DNA methylation patterns (Joubert et al., 2012), that also worsen the prognosis in childhood ALL (Borssén et al., 2018). Secondly, SHS increases the frequency and severity of infections in children (Huttunen et al., 2011; Kum-Nji et al., 2006). It is known that infections are the most important cause of TRM in infant ALL (O'Connor et al., 2014; Orgel and Bhojwani, 2017). Kum-Nji et al. (2006) shows that nicotine decreases the phagocytic function of macrophages, inhibits Th-1 helper cells which are responsible for the production of IgG, and stimulates Th-2 helper cells, which increase cytokines and interleukins, generating a chronic inflammatory reaction. In addition, nicotine decreases cellular cytotoxic activity by inhibiting natural killer cells, affects the mucociliary epithelium through direct toxic damage, and increases the adherence of pathogenic bacteria. In this way, exposure to SHS causes an increase in the frequency and severity of infections, including sepsis (Kum-Nji et al., 2006). In our study, persistent maternal smoking is the only risk factor for TRM. All cases of TRM occur in children of smokers (see Fig. 1c), and as we can see in Table 4, 70% of cases of TRM were due to infectious complications.

Another possible mechanism by which exposure to SHS could influence survival would be to stimulate tumor progression. Both nicotine and the activation of nicotinic acetylcholine receptors (nAChR) can increase tumor proliferation, migration and invasion of other organs, angiogenesis, and epithelium-mesenchyme transition (Schuller, 2012; Zhu et al., 2003). In addition, nicotine can also decrease the effectiveness of chemotherapy and radiation therapy, as well as increase the side effects and toxicity of chemotherapy (Gritz et al., 2005).

Finally, children may be exposed to third-hand smoke (THS) due to residues that persist in the home deposited on surfaces (Jacob et al., 2017). Exposure pathways for THS include not only inhalation but also dermal uptake from contact with contaminated surfaces (potentially including the clothing of smokers) and ingestion of THS that is on the hands or on food. For toddlers, mouthing of objects in their environment is another route of potential oral exposure to THS. The time scale for the presence of THS indoors will generally be much longer than that for second-hand smoke and could stretch to months.

A strength of this study is the use of the PEHis questionnaire in order to capture most of the common environmental exposures to children, including environmental tobacco smoke. A careful PEHis can help contribute to the personalization of the prognostic factors by considering an environmental approach. A second strength is its cohort nature and representative sample, including almost 100% of the children diagnosed with ALL in the Region of Murcia for 18 years, which avoids selection bias, in addition the fact that all patients were treated in the same hospital decreases possible bias due to differences in management. Another strength of the study is the long follow-up of the sample analyzed (average of 105.3 months).

The main limitation of our study is the sample size, due to the high percentage of treatment success cases resulting in death are scarce. Besides, since enrollment included children diagnosed over a period of 18 years, there has been different treatment protocols and it seems possible that these differences may have interact with exposures to impact outcomes. Nevertheless, due to the small sample size we were unable to stratify the results by treatment protocol to study this question. In the same way, a larger sample size would have allowed us to evaluate the effect that SHS has on the different cytogenetic subtypes. Additionally, the high prevalence of smoking in the Region of Murcia and Spain may have contributed to the observed results. Although only SHS data has been used for this work, other environmental exposures could act as potential confounders and will be analyzed in the future. Other classic limitations of studies where smoking history is collected through questionnaires are the biases of information collection and memory. To minimize this bias, the information was collected, as stated above, using the PEHis questionnaire, through face-to-face personal interviews with both parents at the beginning of the treatment conducted by health personnel trained in environmental health and risk communication in childhood cancer and verifying the information with the medical records. Finally, in studies of passive exposures to environmental tobacco smoke, another limitation is the possible lack of correlation between the consumption of tobacco by parents and exposure in children. In our study no quantification of nicotine metabolites was performed. However, Whitehead et al. (2009) assessed the suitability of the tobacco history collection interviews in 469 homes of children with childhood leukemia and controls and found that estimates of exposure by questionnaires correlated strongly with the levels measured in house dust samples.

Taking into account the results as well as the limitations of our study, we would like to encourage international groups to expand and help reproduce results in multicenter studies inside and outside the ENSUCHICA network. Future work should further refine prognostic factors, such as environmental tobacco smoke, to best understand when and how to intervene and thereby improve ALL prognosis. What is encouraging about this study is that SHS is a modifiable and preventable prognostic factor that seems to decrease the OS of the ALL. In the future, we think that the development of personalized medicine will be accompanied by the study of individualized prognostic factors as well as assessment of the patient's environment. Meanwhile, it seems sensible to consider parental smoking cessation as first-line therapy in treatment protocols for ALL to improve the survival of children diagnosed with leukemia and, as a result, to promote a higher environmental quality in the family environment that preserves the health of all the members of the family.

5. Conclusion

Prognosis and survival related to ALL depend on numerous factors such as children's medical history, stage of the disease, treatments and response to treatment. Our study finds that the persistent SHS of children with ALL is a significant predictor of OS, so we deem it necessary to introduce smoking prevention and cessation in families of children with ALL. We recommend that pediatric oncologists consider this aspect of treatment to help improve the prognosis of this disease, pending the increase of scientific knowledge about the causes that originate it and other prognostic factors of interest.

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Human subjects' ethics review

Informed consent was obtained from all parents and this study was approved by the Ethics Committee and the Institutional Review Board at the Clinical University Hospital "Virgen de la Arrixaca" (Murcia, Spain).

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Appendix A. Supplementary data

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