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Survival in France after childhood acute leukaemia and non-Hodgkin's lymphoma (1990–2000)

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ABSTRACT

This article describes the survival after childhood acute leukaemia (AL) and non-Hodgkin's lymphoma (NHL) of French population aged less than 15 years. The French National Registry of Childhood Leukaemia and Lymphoma recorded 3995 cases of acute lymphoblastic leukaemia (ALL), 812 of acute myeloid leukaemia (AML) and 1137 of NHL over the period from 1990 to 2000. Overall survival rates at 5 years were 82% (95% CI 80–83), 58% (95% CI 54–61) and 87% (95% CI 85–89) for ALL, AML and NHL, respectively. Survival after AL increased from 77% (95% CI 75–80) in 1990–1992 to 85% (95% CI 83–87) in 1997–2000 for ALL and from 47% (95% CI 41–54) to 61% (95% CI 55–67) for AML. Among AL cases, children aged 1–4 years had the most favourable prognosis. Down's syndrome was associated with poor survival after ALL. No gender-related variations in survival were in evidence. The results reported herein are similar to those reported by other European registries and clinical trials.

1. Introduction

In France, as is the case in other industrialized countries, acute leukaemia (AL) is the most frequent cancer in children aged less than 15 years.[1] Acute lymphoblastic leukaemia (ALL) accounts for approximately 80% of childhood leukaemia cases. The incidence rate for ALL, standardized on the world population, is 34.3 cases per million children per year with a sex ratio of 1.4 in mainland France.[2] Acute myeloid leukaemia (AML) and non-Hodgkin's lymphoma (NHL) are very rare childhood diseases, with a standardized rate of 7.1 and 8.9 cases per million children per year, respectively.

Over the past 30 years, a remarkable increase in the childhood survival after malignant haematopoietic diseases has been observed in industrialized countries. Non-Hodgkin's lymphoma, which was a fatal cancer before 1970, has become a curable disease in the great majority of cases. In spite improvements in survival of children with acute

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non-lymphocytic leukaemia, survival at 5 years still remained very low in Europe with a rate of 37%[3] at the beginning of 1990s. Survival after ALL increased from 50% in the 1970s to more than 80% in the 1990s.[4] This improvement is particularly due to progress in treatment networks and application of advances in centres specializing in the treatment of childhood cancers.[5]

The aim of this study is to describe the survival of children aged less than 15 years, presenting with acute leukaemia or non-Hodgkin's lymphoma and residing in mainland France, at the time of diagnosis for the period from 1990 to 2000. This is the first French nationwide report on the survival of children with acute leukaemia or NHL. The data were provided by the French National Registry of Childhood Leukaemia and Lymphoma (NRCL).

2. Patients and method

2.1. Case registration

The methods used by the French National Registry of Childhood Leukaemia and Lymphoma (NRCL) to record cases and code diagnoses have been described in detail elsewhere.[2] The NRCL includes all malignant haematopoietic diseases occurring in children aged less than 15 years residing in mainland France at the time of diagnosis. However, Hodgkin's disease has only been recorded since 1999. Cases are actively retrieved from paediatric haematology and oncology departments (about 40 centres). Many children with acute leukaemia and non-Hodgkin's lymphoma are also identified from inclusion lists of clinical trials. Since 1998, many hospital admission departments have also provided the NRCL with lists of children hospitalized for cancer. A non-nominal list of childhood cancer deaths in France is forwarded by the French National Institute of Health and Medical Research (INSERM) department responsible for information on medical causes of death (Cépi-cd). The diagnoses are coded according to the international classification of diseases for oncology (ICD-O-3).

From 1990 to 2000, the NRCL registered 6414 childhood cases of haematopoietic malignancies, including 4914 cases of acute leukaemia (AL) and 1139 of non-Hodgkin's lymphoma (NHL). Lymphomas and myeloproliferative and myelodysplastic syndromes with more than 20% blasts at diagnosis were coded as acute leukaemia. Microscopic diagnosis was available for 98% of the cases. The cytological findings were reported for 99% of the ALL and 98% of the AML. The cytohistologic results were obtained for 98% of the NHL. Three cases identified by death certificate only or discovered during autopsy were excluded from the study. Thirty-seven cases of malignant haematopoietic disease were secondary to a tumour or treatment. Those cases were not included in the survival analyses.

2.2. Vital status

When birthplace was known, the NRCL verified the vital status of each the cases through the administrative unit ("commune") of the place of birth, using a national electronic procedure, completed manually when necessary. Vital status was thus determined for 5652 (94%) of the 6013 cases of AL and NHL. For the remainder of the cases, the last follow-up date was the date of the last consultation reported in the hospital files. From 1990 to 1998, the follow-up duration was greater than 5 years for 99% of the AL and 98% of the NHL cases. For cases diagnosed from 1990 to 2000, the cut-off date was December 31, 2003. At that date, vital status was known for 97% and 89% of the AL and NHL cases, respectively. The mean duration of follow-up was 5.9 years (0–14 years).

2.3. Statistical analysis

The observed survival rates were estimated using the Kaplan–Meier method. The roles of age at diagnosis (<1 year, 1–4 years, 5–9 years and 10–14 years), gender, immunology for ALL, histology for NHL, FAB (French–American–British) type for AML, inclusion in clinical trials and period of diagnosis were analyzed. The log-rank test was used to compare the survival curves of the subgroups. Survival rates have been reported with their 95% confidence intervals in brackets. Multivariate analyses were carried out using a Cox proportional hazard model and the effects of the different variables on survival were estimated by hazard ratios (HR) for those covariates. In order to check the proportionality assumption of the Cox model, cumulative hazard functions ($\log[-\log S(T)]$) were plotted.

3. Results

3.1. Population description

From 1990 to 2000, NRCL registered 4876 cases of acute leukaemia (3995 ALL, 812 AML and 69 unspecified AL) and 1137 cases of NHL as primary cancers.

Table 1 shows the distribution of cases by disease type. For ALL, 57% of the cases were boys and 48% aged 1–4 years, with the expected incidence peak at 2 years. Down's syndrome was present in 65 ALL cases (56 cases with immature B-cells, 7 unspecified ALL, 1 case with Burkitt cells and 1 case with T-cells) and 52 AML cases. AML was as frequent in girls as in boys. For NHL, the male:female ratio was 2. Out of the 1137 NHL cases, 64% had B-cell NHL, of which Burkitt's lymphoma was the most frequent histological subtype (72%). Lymphoblastic T-cell NHL accounted for 77% of the T-cell NHL cases.

The survival rates for ALL were 94% (CI 93–95) at 1 year and 82% (CI 80–83) at 5 years (Fig. 1). Deaths occurred regularly over the period. During the 5 years of follow-up, the survival of AML cases was consistently lower than that of ALL cases. The AML survival rate decreased markedly over the 3 years post-diagnosis, from 93% (CI 91–95) at 3 months to 60% (CI 57–64) at 3 years. Death due to NHL mainly occurred in the 2 years post-diagnosis (125 deaths at 2 years).

3.2. Diagnostic subtypes

Table 2 shows the distribution of leukaemia and lymphoma cases and their survival rates. Acute leukaemia of the M4/5 and M1/2 types was the most frequent, accounting for 36% and 30% of AML cases, respectively. The acute promyelocytic (M3) and myeloblastic (M1–M2) types had the best prognoses

Table 1 – Characteristics of the children registered in the NRCL 1990–2000

	ALL	AML	NHL
	No. (%)	No. (%)	No. (%)
Gender			
Boys	2275 (57%)	410 (50%)	790 (69%)
Girls	1720 (43%)	402 (50%)	347 (31%)
Age (years)			
<1	121 (3%)	132 (16%)	10 (1%)
1–4	1925 (48%)	259 (32%)	231 (20%)
5–9	1209 (30%)	197 (24%)	451 (40%)
10–14	740 (19%)	224 (28%)	445 (39%)
Down's syndrome			
No	3930 (98%)	760 (94%)	1134 (99%)
Yes	65 (2%)	52 (6%)	3 (1%)
Period of diagnostic			
1990–1992	1120 (28%)	217 (27%)	295 (26%)
1993–1996	1451 (36%)	310 (38%)	424 (37%)
1997–2000	1424 (36%)	285 (35%)	418 (37%)
Clinical trials			
No	223 (6%)	279 (34%)	216 (19%)
Yes	3772 (94%)	533 (66%)	921 (81%)
Total	3995	812	1137

ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia; NHL, non-Hodgkin's lymphoma.

Table 2 – Survival after acute leukaemia or non-Hodgkin's lymphoma cases by diagnosis subtype, 1990–2000

	N	5-year survival (%)	log-rank (P value)
AML N = 809			
M0	39	58 [43–74]	$<10^{-4}$
M1/2	243	62 [56–68]	
M3	54	83 [73–93]	
M4/5	293	59 [53–64]	
M6	19	41 [19–64]	
M7	86	38 [28–49]	
NOS	75	48 [37–59]	
NHL N = 1128			
Burkitt	519	92 [90–94]	$<10^{-4}$
Others B	210	87 [83–92]	
Lymphoblastic T	194	79 [73–84]	
Anaplastic	124	86 [80–92]	
Other or NOS	81	76 [67–86]	
ALL N = 3960			
B-cell immature	3123	85 [84–86]	$<10^{-4}$
B-cell mature	159	85 [80–91]	
T-cell mature	596	67 [63–71]	
NOS	82	63 [52–74]	

ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia; NHL, non-Hodgkin's lymphoma; NOS, not specified.

at 5 years, with survival rates of 83% (CI 73–93) and 62% (CI 56–68), respectively. Acute megakaryoblastic leukaemia (M7) [38% (CI 28–49)] and erythroleukaemia M6 [41% (CI19–64)] had the poorest outcomes. Immature B-cell ALL accounted for 95% of B-cell ALL. The survival rate at 5 years [85% (CI 84–86)] was higher than that for T-cell ALL [67% (CI 63–71)]. There were also survival differences between the histological types of NHL. Five-year survival was markedly greater for Burkitt's NHL [92% (CI 90–94)] than for T-cell lymphoblastic NHL [79% (CI 73–84)].

3.3. *Individual characteristics of cases*

Table 3 shows the survival rates at 3 months, 1 year and 5 years for AL and NHL by age at diagnosis, gender and presence/absence of Down's syndrome. Irrespective of follow-up duration, the survival of infants aged less than 1 year was consistently inferior to that of children aged 1–9 years. The 5-year survival of infants aged less than 1 year was 48% for ALL and 45% for AML, while that for children aged 1–4 years was 87% for ALL and 62% for AML. In contrast, the survival of children aged 1–4 years with T-cell ALL was the same as those of the other age groups (67%, 63%, 72%, 62% for less than 1 year, 1–4, 5–9 and more than 10 years, respectively). For NHL, no major variation with age was observed. There was no significant between-gender difference in survival irrespective of follow-up duration or disease subtype. The prognosis was poorest in ALL cases with Down's syndrome, but Down's syndrome did not significantly decrease the survival of the AML cases.

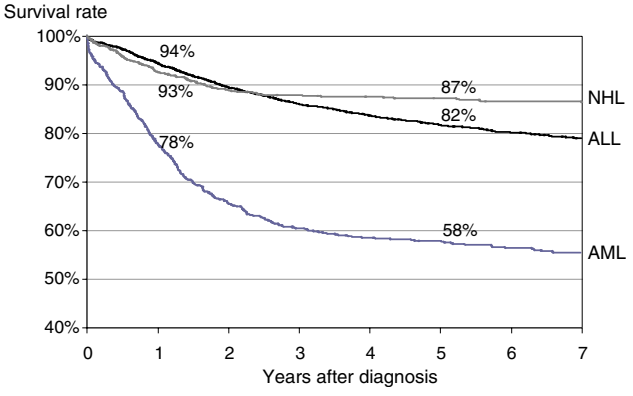

Fig. 1 – Survival curves after childhood leukaemia and non-Hodgkin's lymphoma diagnosis in France (1990–2000).

Multivariate analyses gave similar results (Table 4). The variables included in the model were gender, age, presence of Down's syndrome, period of diagnosis, and FAB type for AML. For ALL, infants aged less than 1 year had a sixfold higher risk of death than children aged 1–4 years [HR = 5.7 (5.4–6.0)]. The AML hazard ratio was also significantly higher for infants [HR = 1.7 (1.4–2.0)] and for cases aged more than 10 years [HR = 1.3 (1.0–1.6)] than for those aged 1–4 years. No significant variation in hazard ratio with age was observed for T-cell or mature B-cell ALL.

3.4. *Inclusion in clinical trial protocols*

Almost all the ALL (94%) and most of the NHL cases (81%) were enrolled in clinical trials between 1990 and 2000 (Table 1). Children with AML were less often (66%) included in trials. Children were enrolled in a clinical trial or reported as trial exclusions, or not included in a trial but nonetheless treated per-protocol. In the latter situation, non-inclusion was considered related to reasons other than clinical or laboratory

Table 3 – Survival after acute leukaemia and non-Hodgkin's lymphoma, by gender, age at diagnosis and presence/absence of Down's syndrome, 1990–2000

	3 months %	log-rank (P value)	1 year %	log-rank (P value)	5 years %	log-rank (P value)
ALL (N = 3960)						
Gender						
Boys	98 [98–99]	0.87	94 [93–95]	0.63	81 [79–82]	0.07
Girls	98 [98–99]		95 [94–96]		83 [81–85]	
Age (years)						
<1	93 [88–97]	$<10^{-4}$	77 [69–84]	$<10^{-4}$	48 [39–57]	$<10^{-4}$
1–4	99 [98–99]		96 [95–97]		87 [85–88]	
5–9	99 [98–99]		95 [94–96]		83 [81–85]	
10–14	97 [96–98]		91 [89–94]		72 [69–76]	
Down's syndrome						
No	98 [98–99]	0.05	94 [94–95]	0.41	82 [81–83]	$<10^{-2}$
Yes	95 [90–100]		92 [86–99]		66 [54–78]	
AML (N = 809)						
Gender						
Boys	93 [91–96]	0.56	78 [74–82]	0.71	56 [51–61]	0.41
Girls	92 [90–95]		77 [73–81]		59 [55–64]	
Age (years)						
<1	83 [76–89]	$<10^{-4}$	61 [53–70]	$<10^{-4}$	45 [37–54]	$<10^{-3}$
1–4	93 [90–96]		80 [75–84]		62 [56–68]	
5–9	97 [95–99]		84 [78–89]		61 [54–68]	
10–14	95 [92–98]		81 [75–86]		57 [51–64]	
Down's syndrome						
No	93 [91–95]	0.06	79 [76–81]	0.06	58 [54–61]	0.58
Yes	87 [77–96]		67 [55–80]		56 [42–69]	
NHL (N = 1128)						
Gender						
Boys	98 [97–99]	0.65	93 [91–95]	0.29	88 [86–91]	0.06
Girls	98 [96–99]		91 [88–94]		84 [80–88]	
Age (years)						
0–4	96 [93–98]	0.02	92 [88–95]	0.81	85 [81–90]	0.13
5–9	98 [97–99]		93 [90–95]		90 [87–93]	
10–14	99 [98–100]		93 [90–95]		85 [82–89]	

ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia; NHL, non-Hodgkin's lymphoma.

criteria (e.g., parent's refusal). The survival of cases included in a trial was not different to that of cases not included but treated per-protocol.

3.5. *Temporal trend*

From the first (1990–1992) to the last (1997–2000) diagnostic period, 5-year survival increased from 77% (CI 75–80) to 85% (CI 83–87) for ALL, and from 47% (CI 41–54) to 61% (CI 55–67) for AML. In contrast to the survival rate for Burkitt's ALL cases, which was already high in the early 1990s, the survival of children with immature B-cell and T-cell ALL improved over the period, increasing from 80% to 88% and from 60% to 71%, respectively. The temporal increase in AL survival remained in the multivariate analysis (Table 4). The temporal variations in AL survival rates are shown by gender, age at diagnosis, presence/absence of Down's syndrome and disease subtype in Fig. 2 (ALL) and Fig. 3 (AML). Improvements in survival were observed, to a variable degree, in most categories. The NHL survival rates for the periods 1990–1995 and 1995–2000 were similar.

3.6. *Cases per centre*

From 1990 to 2000, 44 hospital departments were responsible for the initial treatment of childhood blood malignancies in mainland France. On average, the departments treated 8 cases of ALL (range: 0.1–34.1), 1.9 cases of AML (range: 0.1–6.5) and 3 cases of NHL (range: 0.1–9.7) per year. When centres treating less than 5 cases per year were compared with those treating 5 or more cases per year, there was no significant difference in survival: 79% (CI 75–83) vs. 82% (CI 81–83) for ALL, 56% (CI 52–60) vs. 62% (CI 55–68) for AML and 86% (CI 84–89) vs. 88% (CI 85–91) for NHL.

4. Discussion

This study was the first to analyze childhood AL and NHL survival in France on a national scale. The strength of the study resides in the high proportion of cases with microscopic diagnosis and complete follow-up, and the completeness of NRCL recording (99% for leukaemia and 97% for NHL). The authors previously reported[2] that the characteristics of the French

Table 4 – Multivariate survival analyses of AL cases in France, 1990–2000 – Cox analyses including gender, age, presence/absence of Down's syndrome, diagnosis period and FAB subtype for AML

	ALL		B-cell immature ALL		AML	
	HZ	95% CI	HZ	95% CI	HZ	95% CI
Gender						
Boys	1.0	Ref.	1.0	Ref.	1.0	Ref.
Girls	0.9	[0.7; 1.1]	1.0	[0.8; 1.2]	1.0	[0.8; 1.2]
Age (years)						
<1	5.7	[5.4; 6.0]	7.0	[6.7; 7.3]	1.7	[1.4; 2.0]
1–4	1.0	Ref.	1.0	Ref.	1.0	Ref.
5–9	1.3	[1.1; 1.5]	1.3	[1.1; 1.5]	1.1	[0.8; 1.4]
10–14	2.4	[2.2; 2.6]	2.6	[2.4; 2.8]	1.3	[1.0; 1.6]
Down's syndrome						
No	1.0	Ref.	1.0	Ref.	1.0	Ref.
Yes	2.3	[1.9; 2.7]	2.9	[2.4; 3.4]	0.8	[0.3; 1.3]
Period of diagnosis						
1990–1992	1.0	Ref.	1.0	Ref.	1.0	Ref.
1993–1996	0.8	[0.6; 1.0]	0.7	[0.5; 0.9]	0.7	[0.4; 1.0]
1997–2000	0.6	[0.4; 0.8]	0.5	[0.3; 0.7]	0.7	[0.4; 1.0]
FAB subtype						
LAM					1.7	[1.3; 2.1]
LAM0					1.1	[0.6; 1.6]
LAM1/2					1.0	Ref.
LAM3					0.4	[−0.3; 1.1]
LAM4/5					1.1	[0.8; 1.4]
LAM6					1.5	[0.9; 2.1]
LAM7					2.1	[1.7; 2.5]

AML, acute myeloblastic leukaemia; ALL, acute lymphoblastic leukaemia.

cases (sex ratio, age distribution and presence/absence of Down's syndrome) were similar to those of other European cases. The present study did not address white blood cell count, a known prognostic factor for ALL[6–8] that is used in risk assessment, since that variable was not recorded by the NRCL.

Relative survival was not estimated since competing causes of death in childhood are very rare in developed countries. In this situation, relative survival is very close to observed survival.

4.1. *Survival estimations and temporal variations*

Overall, survival improved over the whole period, 1990–2000. These positive trends reflect therapeutic progress: combination chemotherapies, larger scale use of bone-marrow transplants for AML, and adaptation of treatment intensity to the severity of the disease.[9,10] Several European cancer registries have reported this temporal survival trend for periods before[3,11–13] or during[6] that considered herein. In the United States, SEER noted a similar increase in survival for AL.[14] Between 1970 and 1990, the prognosis of NHL improved in Europe[15] and United States,[14] as treatments took into account disease staging and histological subtype.[16,17] Following that marked increase, the 5-year survival after NHL seems to have reached a plateau at close to 90%. However, a significant positive trend in survival throughout the period 1990–2000 was observed for the lymphoblastic T-cell NHL subtype [from 72% (CI 64–81) in 1990–1995 to 85% (CI 78–92) in 1995–2000]. The French 5-year survival rates estimated by the NRCL were similar to those estimated by the Italian and UK registries[6,18] and ACCIS,[19] as well as by recent large-scale European clinical trials.[7,20–22]

For AML, contrasting survivals were observed, with the highest rate for subtype M3 and the lowest for subtype M7, similar to that reported in previous studies.[3,23]

4.2. *Gender*

In the present data, gender did not affect AL survival. For ALL, this finding is not consistent with previous studies[12,18,24] that reported a more positive outcome for girls. Some authors have suggested that the difference was partially explained by the differences in the distributions of immunophenotype and DNA index, or by different biological mechanisms of reaction to treatment, depending on gender. With regard to AML, the result reported herein is consistent with several studies.[11,25,26] Two other studies have reported superior survival for girls, but no biological mechanism has been suggested as an explanation.[3,27]

4.3. *Infants*

The poor survival of infant AL cases aged less than 1 year is consistent with most cancer registry studies[3,12,6,18] and clinical trials.[7] In line with the Pediatric Oncology Group (POG 8691 and 8704),[28] this study did not evidence any between-age-group difference in T-cell ALL survival. For AML, a marked increase in the survival of infants aged less than 1 year was observed throughout the period [90–95: 33% (CI 21–44) vs.

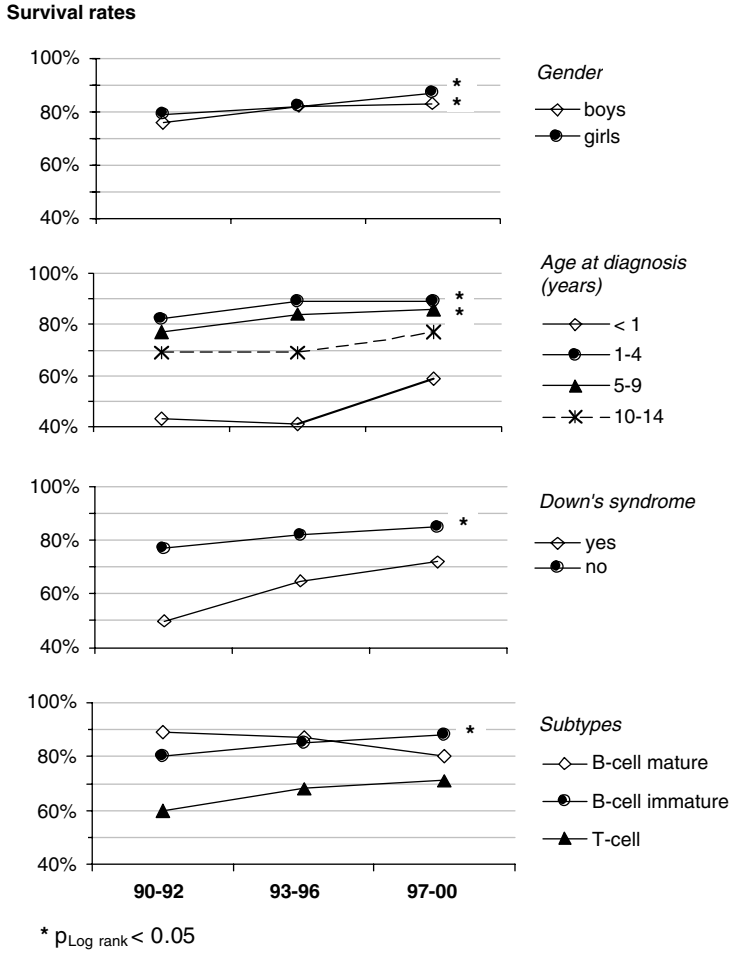

Fig. 2 – Variations in ALL survival rates by diagnosis period.

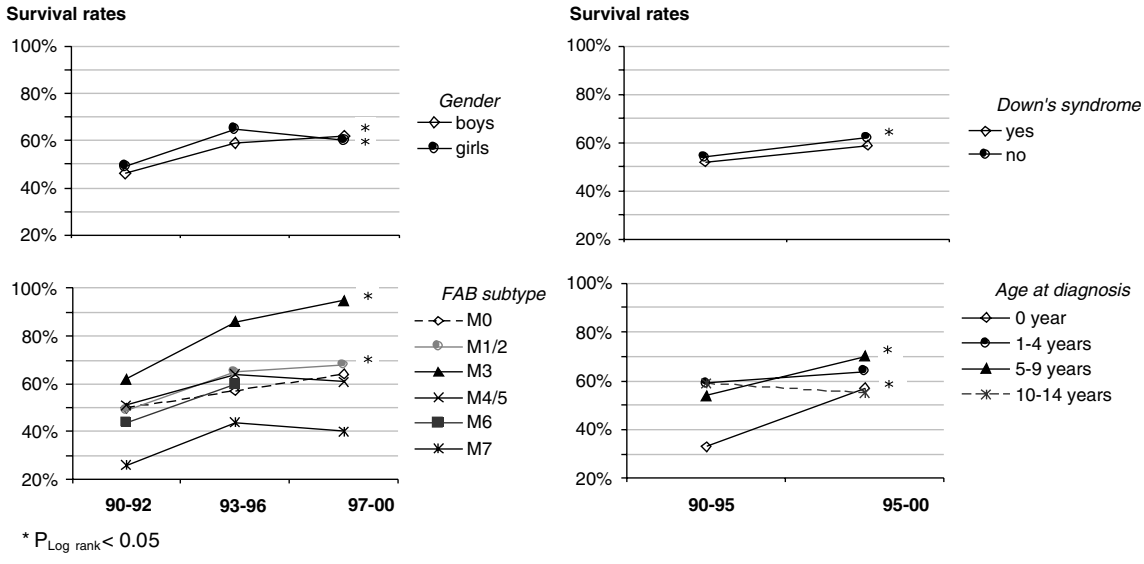

Fig. 3 – Variations in AML survival rates by diagnosis period.

95–100: 57% (CI 46–69)]. In the last period, infants had a prognosis that was as good as that of other children ($P = 0.09$). This improvement in survival has also been observed in clinical trial protocols: age less than 1 year was not an adverse prognostic factor in the LAME 89/91[29] or AML10 and AML12[21] trials.

4.4. *Down's syndrome*

As has been previously reported, survival was lower for children with ALL and Down's syndrome than for those without the syndrome, although survival tended to improve between 1990 and 2000. As two studies from United Kingdom[11,30] have pointed out, in AML with Down's syndrome the survival is similar to that observed in AML without the syndrome thanks to adaptation of chemotherapy to the patient's sensitivity.[31]

4.5. *Cases per centre*

In the present study, the number of cases treated by hospital department (<5 or ⩾5) did not influence survival. In the United Kingdom during the 1980s, similar results were reported for children with ALL.[18] In France, the homogeneity of survival is doubtless due to the fact that all cases are treated in specialized departments in which standardized patient care patterns are implemented irrespective of the number of cases treated. The proportion of children enrolled in clinical trials was similar and high (88%) in all hospital departments and this might explain the homogeneity in survival.

The incidence and survival rates determined by the NRCL are similar to those reported by other European registry studies and clinical trials. For most AL, survival clearly increased over the 1990–2000 period.

Conflict of interest statement

The authors disclose no financial and personal relationships with other people or organizations that could inappropriately influence their work.

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