# Symptomatic osteonecrosis in French survivors of Childhood and Adolescent Leukemia: a clinical and radiological study from the L.E.A. program

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**Abstract**

Background. Osteonecrosis (ON) is a long-known complication of acute leukemia (AL) management affecting 1 to 10% of young patients, leading to long-term morbidity. Widespread access to Magnetic Resonance Imagery (MRI) over the past ten years has allowed earlier detection and more accurate assessment. This study investigated clinical and radiological features of ON, among the large French cohort L.E.A (Leucémie Enfant Adolescent) Procedure. Patients with ON were retrospectively enrolled and risk factors for the onset, the multifocal involvement and severe damage were analyzed. Quality of life (QoL) was also evaluated. A sub-study described radiological features. Results. 129/4973 patients developed ON (2.5%) and were preferentially aged over 10 years at time of AL diagnosis (OR 22.46, p <10-6). Females were preferentially affected (OR 1.8, p=0.002) like patients treated for relapse (OR 1.81, p=0.041). Patients presenting ON suffered more frequently from other sequelae (p<10-6).

Most of the necrosis were involving weight-bearing joints and multiple joints in 69% of cases. MRI of 39 patients with ON were double blinded reviewed. Overall, 14/39 suffered from severe impairment, preferentially on hips. QoL of adolescents and adults was poor and permanently affected once ON occurred. Conclusions. Age of over 10 years at diagnosis of AL, relapse and female sex were at risk of developing ON involving preferentially multiple joints. One third was severe and lasting poor QoL impacting several domains was found. Future studies should include prospective data on management and biological genetic features to build a targeted screening program to detect and manage ON earlier.

# INTRODUCTION

Acute leukemia (AL) is the most common cancer in children[1]. Major therapeutic advances have been made over the past twenty years, as 80% of children with acute lymphoblastic leukemia (ALL), and 60% of those who have acute myeloid leukemia (AML) now recover from their disease [2].

Osteonecrosis (ON) is a long-known complication of leukemia[3,4]. Local ischemia due to compromised blood flow is the final common pathway in the pathogenesis of ON. Ischemic lesions do not always lead to irreversible bone necrosis if there is a restoration of vascular perfusion [5]. Glucocorticoid is one of the most known involved factors for ON, particularly dexamethasone, by a kind of intraosseous compartment syndrome starting with an hyperplasia of marrow fat cell to intra-osseous hypertension causing an impaired blood flow [6,7]. An increased exposure to corticosteroids in ALL treatment has led to an increase in ON levels this past decades [8–11].

ON incidence is estimated at 1.5% after treatment with chemotherapy, and between 5 and 10% after allogeneic hematopoietic stem cell transplantation (HSCT) [12,13]. It increases to 17.6% when diagnosed on routine imaging [14]. In 2013, among the 943 patients already included in the L.E.A (Leucemie Enfants Adolescents) program, a study of 24 patients with ON showed that being over 10 years old at AL diagnosis, the achievement of a stem cell transplant (SCT) and a cumulative high levels corticosteroid favored the onset of ON [12].

Ease of access to MRI for fifteen years has allowed a more precise and earlier diagnosis of ON disorders and opens the possibility of less invasive therapeutic management, limiting the long-term sequelae. In addition, two major works to harmonize the radiological classification, regardless of the injured joint, and to better define ON were carried out in 2015 by Niinimäki et al [15,16] and the Ponte di Legno group [17]. In this context, while nearly 4000 patients have been included in the L.E.A program over the last 6 years, we performed a novel study to describe clinical and radiological ON occurring during the treatment of AL in childhood. Our secondary objectives were to explore the risk factors for the onset of ON, to analyze the predictive factors of having multifocal damage and / or severe damage on MRI at diagnosis. In addition, we also evaluated the impact of ON on QoL of patients who reached adulthood.

# METHODS

We analyzed all the patients included on June 11, 2019, in the L.E.A program (clinicaltrials.gov identifier: NCT 01756599). This is a national cohort initiated in 2003 to assess the long-term health of patients who were treated in childhood or adolescence for AL, from 1980. The precise functioning of the cohort has already been defined previously [18]. Briefly participants are summoned to a follow-up clinic at predefined dates, starting one year after SCT or after completion of chemotherapy. These visits continue every two years until the age of 20 and at least 10 years of complete remission (CR), and every four years thereafter. Late effects were detected by physicians through regular visits to reference centers, comprising a medical examination and adequate additional tests. Thus, fourteen late effects were prospectively assessed in the entire cohort in which ON was diagnosed.

All patients (or their parents) provided written informed consent. This study was approved by the Sud Méditerranée V ethics committee (opinion n° 2012-A00984-39), in compliance with the General Data Protection Regulation.

We divided our study in two parts. The first study was conducted on all patients with a symptomatic ON identified in the L.E.A. program, to identify the risk factors for the occurrence of this complication, as well as those for having multifocal involvement at diagnosis, and to evaluate the impact of this side effect on long term QoL

The second one focused on radiological assessment for patients who met the following criteria: presence of symptomatic ON with a MRI performed at diagnosis and available for centralized double blinded review at time of the study by 2 experienced pediatric radiologists. The proofreading was performed independently by these radiologists.

The positive diagnosis of ON was retained in the presence of a serpiginous borderline in T1 hypointense delimiting the necrosis area, joining the subchondral bone lamina for epiphyseal damage.[19] The parameters concerning the location and extension of the necrosis were collected in order to classify each location of symptomatic ON according to a grade of severity in accordance with Niinimäki's classification [16] (see Appendix 1) : site of necrosis (epiphysis, metaphysis or diaphysis), bearing character of the joint, affected articular or epiphyseal surface, presence of joint deformation. Were also listed parameters which are known to potentially modify the prognosis [20]: presence of bone edema associated with the periphery of the necrosis area, presence of intra-articular effusion, other ON locations or distant bone marrow edema in the field of exploration, growth cartilages fusion and signal in T1 of the necrosis range (variable depending on the course, initially fatty then progressing to fibrosis).

In the event of disagreement on the severity grade, a joint review was carried out and a consensus was reached. Radiological severity was defined by the presence of V grade, i.e., joint deformity. In the event of multifocal involvement, we have chosen to consider the most severe impairment.

Quality of life of children and adolescents was assessed using the parents' version of the Vécu et Santé Perçue de l'Adolescent et l'enfant (VSP-Ap) which is completed by the parents of the children and adolescents [21–23] . The questionnaire is comprised of nine dimensions and a summary score. All scores range between 0 and 100, with higher scores indicating a better Health Related Quality of Life (HRQoL). Reference values are available for the general French population $> 7$ years of age for sex- and age-matched comparison purposes [22,24]. Adult patients were asked to complete SF-36 questionnaires which consists of 36 items. Results are divided into eight sub scales and two calculated composite scores (physical and mental composite score). The reliability of this scale both in survivors of childhood cancers and in its French version has already been validated [25]

## Statistical methods

The data collected is presented in the form of counts and percentages for the qualitative variables and in the form of means and standard deviations for the quantitative variables. The normality of the distribution of quantitative variables was verified. Chi-square tests or Fisher's exact tests made it possible to compare the qualitative variables according to the different groups of interest. For the quantitative variables, these comparisons were made by Student's tests.

Logistic regressions were carried out, making it possible to model: the risk factors for the onset of ON, multifocal and severe involvement. First univariate analyzes were performed. Variables whose p-value was less than 0.05 in the univariate analysis were retained for the multivariate analysis; a descending step-by-step selection was then carried out. Only the significant variables below the significance level (p-value $< 0.05$) were maintained in the final multivariate model. All analyses were carried out with a significance level of 0.05. Analyses were performed using IBM SPSS Statistics Version 20 software.

HRQoL scores of our patients were compared with the French reference scores for age and sex using paired

Student's t-tests. The calculation of inter-observer reproducibility was determined by kappa statistics between raters, and the results was interpreted according to guidelines adapted from Landis and Koch. [26]

# RESULTS

## Study 1: symptomatic ON

### Characteristics of studied cohort

Among 4973 childhood leukemia survivors included in the L.E.A cohort on June 11, 2019, 129 (2.5%) had suffered from a symptomatic ON and all of them were included in study 1. Among patients with symptomatic ON, 66 had MRI performed for the diagnosis of ON. In 39 patients this MRI was available for central review at time of study n° 2. (Fig. 1).

The detailed characteristics of the 129 patients included in Study n°1 are described in Table 1. The median follow-up time for these patients was 9.97 years and that of the entire cohort was 10.94 years.

ON population consisted of mainly patients with ALL (88%) with a predominance of females (56.6%). Most patients were over 10 years old with a median age of occurrence of 13.3 years. One third of the patients received an allogeneic SCT prior to the onset of bone necrosis. Overall, 69% of patients had a multifocal involvement at ON diagnosis. The median time to onset of ON was 1.8 years after AL diagnosis. Among patients who received a SCT, necrosis was diagnosed on average 1.4 years after the transplantation.

### Risk factors for osteonecrosis and determinants for multifocal character

We analyzed our cohort, after excluding the 365 patients treated for AML without SCT, since none of these patients had bone necrosis.

As a first step, we performed a comparative analysis of the 129 patients with ON with the 4479 patients of the L.E.A cohort without ON in univariate (Supplemental Table S1) and further in multivariate analysis (Fig. 2). SCT was associated with a higher risk of ON in univariate analysis (4.8% of ON for transplanted patients versus 2.3% for those not, $p < 0.001$), but no longer in multivariate analysis (OR 1.29, 95%CI [0.82-2.05], p=0.269). In univariate analysis, BMI at diagnosis (Z score) was also significantly associated with ON in the group of ALL without SCT (p=0.008) but no longer in multivariate analysis (OR 1.08, 95%CI [0.94-1.24], p=0.2). By contrast in multivariate analysis (Fig. 2), we showed that the diagnosis of AL after the age of 10 years was associated with a higher occurrence of ON (OR 22.46, 95%CI [13.8 -36.55] $p < 10^{-6}$). Females were also more often affected by ON (OR 1.8, 95%CI [1.23-2.58] p=0.002), but this predominance disappeared into the group of transplanted patients (OR 1.49, 95%CI [0.7-3.13], p=0.29). We finally highlighted that the presence of a relapse was associated with a more frequent occurrence of bone necrosis (OR 1.80, 95%CI [1.02-3.16], p=0.041).

In addition, we showed in the subgroup of patients who received a SCT (Fig.2B) a higher incidence of ON in patients over 10 years of age and who presented with chronic GVHD. We did not find any evidence of an increased risk of ON according to irradiation use.

In a second step, we looked for risk factors for multifocal involvement in our study population (Table 2). Multifocal involvement was not associated with a particular patient profile, but it was the most frequent presentation occurring in 89/129 (69%) patients suffering from ON.

We were also able to demonstrate that patients who presented ON were also those who were more likely to suffered from multiple sequelae ($p<10^{-6}$) (Supplemental Table S2)

**Quality of life**

First, we compared the last assessment of QoL of patients with osteonecrosis with that of the general French population and of the L.E.A cohort, separately for adults, according to the SF-36 score (Fig. 3A), then for adolescents, according to the parents VSP-A score (Fig. 3B).

We obtained a QoL assessment for 88.7% of L.E.A patients (4088/4608), and for 118 of the 129 osteonecrosis patients. Data was collected from VSP-A parents score for 2087 patients of L.E.A, and 15 patients with ON, and from SF-36 for 1983 patients of L.E.A, and 103 patients with osteonecrosis. In comparison with the general adult population, ON led to a decrease in each parameter of the SF-36 score: physical (74.26 vs 94.76, p $<10^{-6}$), social (73.14 vs 83.97, p<0.001), and emotional well-being scores (67.51 vs 87, p $<10^{-6}$). Furthermore, this negative impact on QoL is also shown when comparing with patients of the L.E.A cohort, for most of parameters except mental health and emotional scores. (Fig. 3A)

These statements were also found when comparing adolescents with their healthy peers, mainly through a physical (physical well-being 44.16 vs 69.97, p=0.002) and friendship impact (48.93 vs 66.86, p=0.005) (Fig. 3B)

Secondly, we looked for the evolution of the QoL of patients with osteonecrosis during their lifetime. We therefore compared the results for the 37 patients for who two assessments of SF-36 questionnaire were available at two different times: first assessment after ON diagnosis with the last available assessment (Fig. 3C). The median time between these two evaluations was 45.6 months [11.6-127]. There was no difference in QoL score with time from ON diagnosis suggesting that the poor impact of ON on QoL occurred soon after ON and lasted.

## Study 2: radiological description of joint damage at diagnosis

Pain was the main symptom identified in medical records as a diagnostic call point for ON, leading to the ordering of an initial standard radiography sometimes followed by an MRI.

Fifty-one patients were excluded for lack of MRI performed. Most of these suffered from osteonecrosis diagnosed before 2009 (40/51 = 72.5%), and for all before 2015. Twenty-seven MRI could not be read even though they had been performed, in connection with default of imaging storage since half of them were carried out before 2009, when a storage tool was generalized in French hospitals. Finally, radiological analysis could be performed for 39 patients, on 63 joints. Our radiological results mainly concerned patients whose leukemia was diagnosed after January 1, 2009: 32 patients out of 39 patients, which corresponded to 69% (32/46) of all patients diagnosed during this period. The characteristics of the 39 patients were not significantly different from those of the 90 patients who had no initial imaging of their necrosis, except for the delay between AL diagnosis and ON which was shorter for the patients included in the study n°2. (Supplemental Table S3).

For the 63 joints analyzed by MRI, we observed only 6 unconformities between both radiologists, which corresponded to a good inter-observer reproducibility with a kappa coefficient of 0.854. Radiological findings per joints and per patients are available in Supplementals Tables S4A and S4B.

The most often affected joints were the weight-bearing ones: knees and hips, with radiological involvement of more than one joint from the time of ON diagnosis in 56.4% of cases: 20 patients had bilateral involvement and 2 patients had multiple joint osteonecrosis (illustrated in supplemental fig.1).

Radiological severity was defined by the presence of V grade, i.e. joint deformity according to Niinimäki's classification [16]. Among the 14 patients with severe involvement, 8 had multifocal involvement. The hips injuries were more often severe (p =0.003) at the time of diagnosis of ON (Table 3). There was also a correlation between radiological severity and surgical management since patients with grade V disease, have more often benefited from joint replacement by prosthesis. (57.14% vs 16%, p = 0.012)

MRI follow-up was performed for 11 patients (28%), with a median delay of 10.9 months between the 2 imaging. There was a stage change for the same articulation on the follow-up MRI for only 2 patients, in

whom stage IV worsened to stage V. Data are available in Supplemental Table S5.

# DISCUSSION

Our study on osteonecrosis was carried out on one of the largest cohort of children and adolescents followed for leukemia, and it was the first radiological study conducted in pediatrics on such a population. We demonstrated that osteonecrosis in the follow-up of childhood acute leukemia was a rare complication (2.5%) except for children over 10 years at the time of diagnosis (10.6%). Early access to MRI allowed characterization of the lesions which were most often multifocal at diagnosis. Moreover, the occurrence of osteonecrosis had a global and rapid negative impact on quality of life which lasted in adulthood.

The incidence of symptomatic ON remained similar (2.8% in 2019 vs 2.5%) [12] in comparison with the L.E.A. 2013 study but the current size of the cohort made the exploration of the risk factors of occurrence and consequences on QoL more relevant.

We confirmed that being a female older than 10 years and suffering from ALL increased the risk of ON [8,12,27,28]. The absence of ON in AML patients who did not undergo SCT could be explained by shorter treatment not involving corticosteroid therapy. Whereas an hormonal role on the occurrence of ON has been described[14] in literature, the lack of significance of the gender in the transplanted population could be explained by two factors: the major role of overall metabolic disturbances induced by the transplant and the possible lack of vigilance for post-transplant hormonal substitution in female for the oldest patients. We also confirmed in our large cohort the impact of chronic GVHD[12]. We did not evaluate in our current cohort the cumulative steroid dose because its role in ON occurrence was well described in various studies but we can speculate that the negative impact of an history of relapse could be in part due to an higher cumulative steroid dose [5,9,10].

Furthermore our study showed for the first time on an homogeneous population that children who received treatment against leukemia, presented with multifocal joint involvement (mainly weight-bearing joints) at ON diagnosis while in other systemic pathologies, such as sickle cell anemia, also known for the frequent occurrence of osteonecrosis, involvement is predominantly unifocal (80% of cases)[29]. This is probably due to corticosteroid therapy, since Kuhlen *et al* has shown it in adult population[30] and Krez e*t al* also showed that a high cumulative dose of glucocorticoids was associated with a risk of multifocal disease in patients with different underlying conditions like systemic lupus erythematosus [31].

We also described the continuing negative impact of the occurrence of osteonecrosis on physical, social, and psychological scores. The absence of changes in QoL between the onset of ON and the last assessment suggests that QoL was permanently impaired as soon as ON occurred. The weak therapeutic arsenal, represented mainly by chirurgical joint prosthesis [32], could explain the lack of possible improvement in the quality of life in these patients.

Finally, our study gave new insights about radiological presentation of ON in the context of leukemia. The widespread access to MRI since 2009 has allowed a representative description of more than 70% of patients with osteonecrosis. We chose to exclude the re-reading of the images of the patients who benefitted from MRI with a delay longer than 6 months (10%) to avoid the risk of lesion modification over time. Because a minor stage change for the same articulation on the follow-up MRI was found in only 20% of patients, we could probably include them in a further study. The centralized blinded proofreading by two radiological experts was a strength of our study. They could correct the diagnosis of osteonecrosis for 3 patients whose MRI lesions were osteochondritis, an isolated diaphyseal infarction and an inflammatory arthritis. The rare disagreements during the re-reading of the MRI have always been linked to images that were difficult to interpret due to a lack of sequences, when the measurement of the affected joint surface was very close to 30%.

We found mainly severe multifocal radiological damages probably because we included only symptomatic ON.

We questioned here the interest to perform systematically a whole joint MRI for searching other damaged but asymptomatic joints in the aim to detect milder lesions and preserve the joint destruction. The radiological diagnosis of these asymptomatic joints could then result in a need for restrictive care like discharge by crutch or wheelchair, balneotherapy and physiotherapy sessions while the patient is not in pain. The benefit of this early diagnostic imaging remains to be demonstrated by a novel study. Our study also raised the issue to perform systematically whole weight bearing joint MRI for children over 10 years old, especially for females with multiple sequelae. The radiological follow-up of these asymptomatic patients should be analyzed in a prospective study to find out whether they progress to regression of the MRI stage. Indeed, Inaba showed recently that MRI at the end of induction of ALL treatment could identify susceptible patients who could benefit of an extensive follow-up imaging and early medical intervention [33] but this study should be confirmed.

Our retrospective study had two main limits: the frequent absence of available MRI for the ON diagnosed before 2009 which limited the size of the study n°2 and the lack in the L.E.A registry of data of accurate information on medical intervention, the use of physiotherapy or discharge for the ON. We were not able to conclude that medical intervention has an impact by the retrospective nature of our study. Prospective data about treatment are essential to establish management recommendations in the future as well as biological insights. Since not all patients exposed to the same treatment will develop ON, we can assume that pathophysiological mechanisms are underpinned by genetic polymorphisms. Some studies go in this direction, with an impact of the nucleotide polymorphisms of the plasminogen activator inhibitor 1-gene, or glutamate receptor GRIN3A [34,35]. The nested case control French GENLEA01 study (Genome-wide association studies GWAS identification of genetic factors affecting the occurrence of late side effects in childhood leukemia survivors from the L.E.A cohort) could help to solve these questions in the future.

**CONFLICT OF INTEREST**

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# LEGENDS

**Figure 1.** Flow chart of the whole study

**Figure 2.** Risk factors for osteonecrosis. Multivariate analysis.

**2A** . All patients

**2B.** SCT patients

**2C.** Patients without SCT

Being over 10 years old when diagnosed with leukemia is associated with a greater occurrence of ON, as well as suffering from relapse due to prolonged treatment. Girls were also often affected, except in the SCT group.

**Figure 3.** Evaluation of quality of life in patients with osteonecrosis.

**3A.** Comparison of adult quality of life with the general population and L.E.A cohort, according to SF-36 score

Comparing to general population, adults have a significant loss in physical global score, social functioning ($p < 0.001$) and emotional global score ($p< 0.001$). This negative impact is also shown when compared with patients of L.E.A cohort, except for mental health and emotional scores.

*Considering the last assessment available for osteonecrosis patients and L.E.A cohort*

**3B.** Comparison of adolescent quality of life with the general population and L.E.A cohort, according to parents VSP-A score.

Comparing to their peers, adolescents have a significant loss in physical well-being ($p=0.002$) and friends scores ($p=0.004$), as the patients of L.E.A cohort ($p=0.019$).

*Considering the last assessment available for osteonecrosis patients and LE.A. cohort. Global score is not considering sentimental life*

**3C.** Evolution of quality of life according to SF-36 score between ON diagnosis and last assessment.

After diagnosis of osteonecrosis, QoL is impaired, but no change over time is observed in the alteration of scores.

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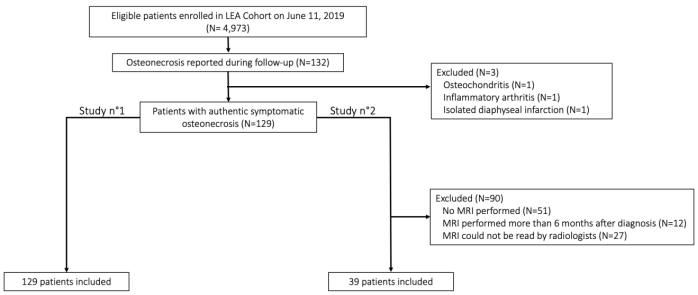
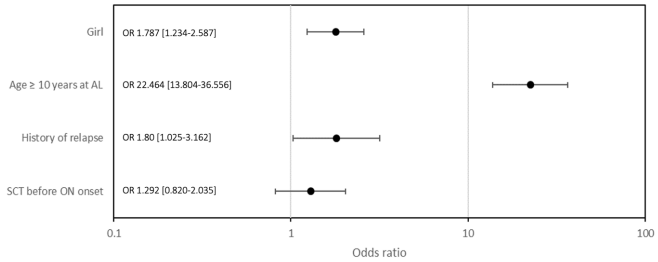
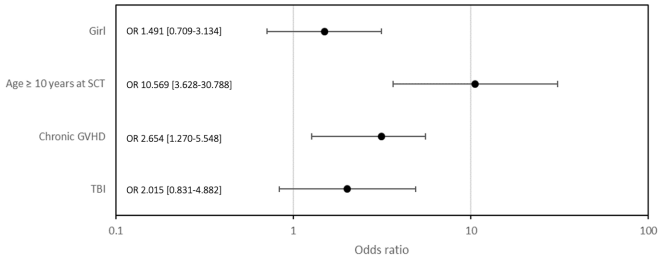


Figure 2. Risk factors for osteonecrosis. Multivariate analysis.

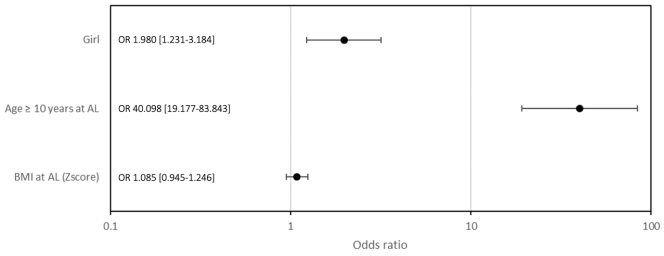
A- All patients (n=4600)




B- SCT patients (n=511)




C- Patients without SCT (n-3663)




AL, acute leukemia; SCT, stem cell transplant; ON, osteonecrosis; GVHD, graft versus host disease; TBI, total body irradiation; BMI, body mass index

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