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Review Article

Outcome of Relapsed Acute Myeloid Leukemia (AML) in Children According to Duration of First Complete Remission

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Summary

Between a third and a half of children treated for acute myeloid leukaemia relapse, and the length of the first remission has long been the variable clinicians reach for when estimating what salvage can achieve. It does predict outcome. What the larger studies show is that it is no longer the best available predictor.

Objectives: To review the published evidence on outcome after first relapse of paediatric acute myeloid leukaemia stratified by duration of first complete remission: how the early and late thresholds were derived, what each predicts for second remission and survival, and how the measure compares with response to reinduction.

Material and Methods: Narrative review of cooperative group relapse trials, registry analyses and single-institution cohorts indexed in PubMed and the major haematology and paediatric oncology journals. Studies were eligible if they reported outcome after relapse of paediatric acute myeloid leukaemia stratified by remission duration or by response to salvage. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: In the largest international relapse trial, second complete remission was achieved in 62 to 63 per cent of patients after two courses of fludarabine-based reinduction. Two-year survival was 38 per cent (SE 9) for early relapse against 54 per cent (SE 7) for late relapse, with 33 per cent (SE 5) for the cohort as a whole. Achieving second remission was the dominant determinant: three-year survival was 47 per cent in those who did against 8 per cent in those who did not. Across the wider literature, three to five-year survival is 10 to 28 per cent after relapse within 12 to 18 months and 40 to 48 per cent thereafter. Response to reinduction stratified more finely than timing: marrow blasts at day 28 of 5 per cent or less, 6 to 10, 11 to 20 and above 20 per cent corresponded to four-year survival of 52, 36, 21 and 14 per cent ($p < 0.0001$), while day 15 status showed no such gradient.

Conclusion: Remission duration is a genuine prognostic factor and an unmodifiable one, known before any salvage decision is taken. Response at day 28 after reinduction separates outcomes across a wider range and is measured at the point where treatment can still change, which makes it the more useful of the two.

Abbreviations: AML – Acute Myeloid Leukaemia, CR1 – First Complete Remission, CR2 – Second Complete Remission, FLAG – Fludarabine, Cytarabine and Granulocyte Colony-Stimulating Factor, HSCT – Haematopoietic Stem Cell Transplantation, BFM – Berlin-Frankfurt-Münster, COG – Children's Oncology Group, OS – Overall Survival, EFS – Event-Free Survival, pSurv – Probability of Survival, SE – Standard Error, MRD – Measurable Residual Disease.

Keywords: Paediatric Acute Myeloid Leukaemia; Relapse; First Complete Remission; Reinduction; Allogeneic Transplantation

Introduction

Relapse occurs in 30 to 40 per cent of children treated for acute myeloid leukaemia, and historically only about a fifth of those patients survived long term [1,2]. Outcomes in first-line therapy improved substantially across successive cooperative group protocols [3,4,5], but that progress did not translate proportionally into the relapse setting, where survival has moved more slowly [6,7].

The duration of first complete remission has been used as the principal prognostic discriminator in this situation for more than twenty-five years. The reasoning is intuitive: leukaemia that returns quickly is assumed to be intrinsically resistant to the agents that produced the first

remission, while leukaemia returning after several years may respond to the same drugs again [8,9].

That assumption was formalised in the late 1990s when a cooperative group reported that remission duration predicted both the chance of achieving a second remission and long-term survival [8]. Subsequent trials adopted early and late relapse categories, usually divided at twelve or eighteen months from diagnosis, and used them to guide the intensity of salvage and the indication for transplantation [1,10].

This review examines how well that division performs, what the largest international relapse trial found, and whether a measure taken after salvage has begun does better than one fixed before it starts.

Material and Methods

Search strategy: PubMed and the archives of the major haematology and paediatric oncology journals were searched for studies of relapsed childhood acute myeloid leukaemia. Search terms combined paediatric acute myeloid leukaemia with relapse, second complete remission, duration of first remission, early and late relapse, reinduction, FLAG and allogeneic transplantation. Reference lists of retrieved trials and reviews were screened by hand.

Eligibility: Studies were included if they reported outcome after relapse of paediatric acute myeloid leukaemia stratified by remission duration, by response to salvage therapy, or by transplantation status. Studies in acute lymphoblastic leukaemia are cited only where they illustrate the same methodological point and are identified as such. Acute promyelocytic leukaemia, which has a distinct salvage pathway, is excluded in line with the trials reviewed.

Data extraction and handling: Design, cohort size, salvage regimen, the threshold used to define early relapse and reported remission or survival estimates were extracted as published. The threshold is stated alongside every figure, because studies divide early from late relapse at twelve or eighteen months and the two are not interchangeable. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

Where the threshold came from: The foundational analysis reported 134 children with first relapse of acute myeloid leukaemia registered with a cooperative group between 1988 and 1996, of whom 102 received intensive reinduction and were followed prospectively. Complete remission was achieved in 52 of 102 (51 per cent), and 27 children were alive at a median of 2.5 years after relapse [8]. The study concluded that remission duration predicted both the remission rate and long-term survival, and that conclusion has shaped practice since.

Disease-free survival in that cohort varied by post-remission strategy: seven of 16 patients transplanted from a matched sibling donor, one of four after matched unrelated donor transplant, ten of 22 after autologous transplant and five of nine after chemotherapy alone [8]. The numbers are small enough that the comparison between strategies cannot be pressed hard, which is worth remembering given how influential the paper became.

What the international trial found: A prospective randomised study enrolled children and adolescents with first relapse, excluding promyelocytic disease and those over 18 at initial diagnosis, and used two consecutive courses of fludarabine, cytarabine and granulocyte colony-stimulating factor as the reinduction backbone [1,10]. Complete remission was achieved in 62 to 63 per cent after two courses.

Two-year survival was 38 per cent (SE 9) for early relapses and 54 per cent (SE 7) for late relapses, against 33 per cent (SE 5) for the cohort as a whole (Figure 1) [1]. The sixteen-point separation confirms remission duration as prognostic, and the confidence intervals around those estimates overlap enough that it is a gradient rather than a dichotomy.

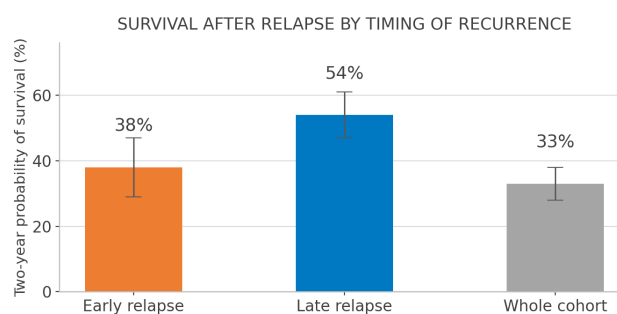


Figure 1: Two-year survival by timing of relapse in the international relapse trial [1]

Achieving second remission is what matters most: The same trial reported three-year survival of 47 per cent among patients who reached second complete remission against 8 per cent among those who did not (Figure 2) [10]. That difference of nearly forty points dwarfs the sixteen-point separation attributable to relapse timing.

The two are related but not equivalent. Remission duration predicts the probability of reaching second remission, which is why it predicts survival at all, but a child with early relapse who achieves second remission has a far better outlook than one with late relapse who does not [1,8,10]. Stratifying by timing alone therefore assigns prognosis before the most informative event has occurred.

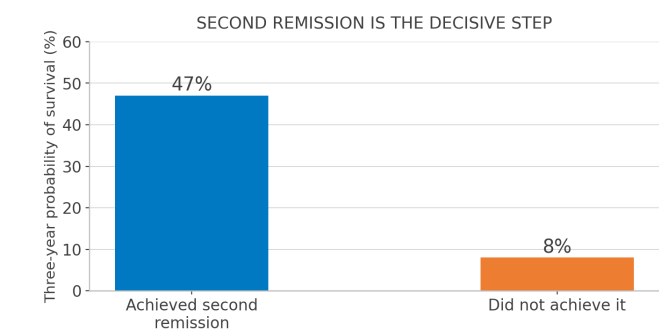


Figure 2: Three-year survival by achievement of second complete remission [10]

Study	n	Focus	Principal reported finding
Stahnke et al. 1998 [8]	134	Remission duration	Duration predicts remission rate and survival
Aladjidi et al. 2003 [11]	—	French cohort	Outcome after relapse following LAME protocols
Rubnitz et al. 2007 [12]	—	Recurrence	Prognostic factors for outcome of recurrence
Kaspers et al. [1,10]	Randomised	Relapsed AML 2001/01	CR 62-63%; survival 38% early against 54% late
Creutzig et al. 2014 [13]	338	Early response	Day 28 marrow blasts stratify four-year survival
Karlsson et al. 2017 [14]	—	Nordic	Outcome after reinduction and allogeneic transplant

Table 1: Principal studies reviewed, with focus and the finding as reported by the original investigators

The wider literature agrees on direction, not on magnitude:

Across published series, three to five-year survival is reported at 10 to 28 per cent for children relapsing within 12 to 18 months of diagnosis, against 40 to 48 per cent for those relapsing later (Figure 3) [13]. Both ranges are wide, and they overlap with the international trial figures without matching them.

Part of that spread is definitional. Studies divide early from late relapse at twelve months in some cases and eighteen in others, and some measure from diagnosis while others measure from the date first remission was documented [8,13]. A child relapsing at fourteen months is early by one convention and late by another, and the groups being compared are therefore not the same groups between studies.

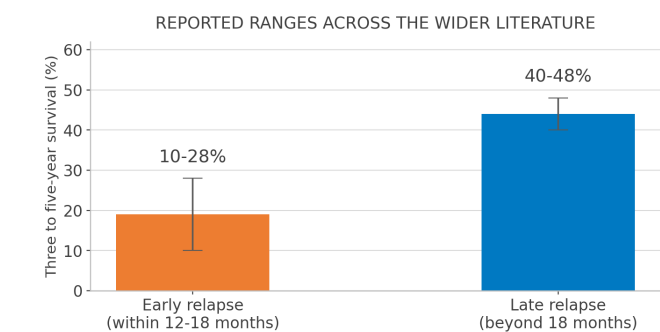


Figure 3: Reported survival ranges by relapse timing across the published literature [13]

Response to reinduction stratifies more finely: The most informative recent analysis assessed marrow blast counts by morphology on days 15 and 28 after the first reinduction course in 338 patients from the international trial. Day 28 status separated outcomes across a wide range: four-year survival was 52 per cent (SE 3) with 5 per cent blasts or fewer, 36 per cent (SE 10) with 6 to 10 per cent, 21 per cent (SE 9) with 11 to 20 per cent and 14 per cent (SE 4) above 20 per cent, $p < 0.0001$ (Figure 4) [13].

Two details make this more useful than the timing categories. The gradient is stepwise across four groups rather than a split into two, and it spans 38 percentage points against the 16 attributable to relapse timing [1,13]. And the same analysis found no equivalent trend at day 15, despite day 15 and day 28 blast percentages correlating significantly, so the informative measurement is specifically the later one [13].

The investigators' stated purpose was to identify a group whose survival could be predicted early and reliably to be below 10 to 20 per cent, as candidates for experimental therapy or for palliation rather than further intensification [13]. Patients with late relapse and a good early response reached only 55 per cent four-year survival, which sets the ceiling for what current salvage achieves even in the most favourable group.

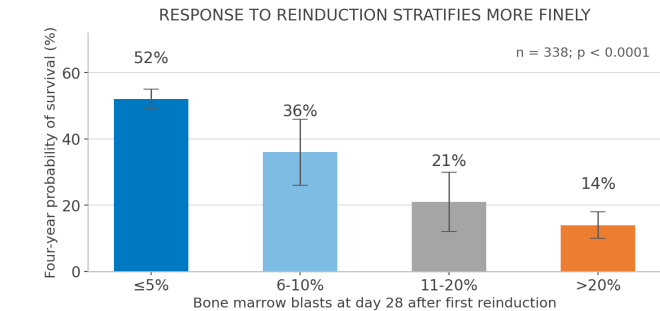


Figure 4: Four-year survival by marrow blast count at day 28 after first reinduction [13]

Measure	Range of outcome	When available
Duration of first remission	38% to 54% at two years [1]	Before salvage begins
Day 15 marrow blasts	No gradient observed [13]	Two weeks into salvage
Day 28 marrow blasts	14% to 52% at four years [13]	Four weeks into salvage
Second remission achieved	8% to 47% at three years [10]	After two reinduction courses

Table 2: Prognostic measures in relapsed disease, the outcome range each separates and when it becomes available

Transplantation and what follows second remission: Current practice is intensive reinduction followed by allogeneic transplantation from a related or unrelated donor [13,14]. Nordic experience has characterised outcome after that sequence specifically [14], and the earlier cooperative group data showed disease-free survival concentrated among transplanted patients, albeit in very small subgroups [8].

Second relapse carries a markedly worse outlook again, and treatment strategies and outcomes at that point have been reported separately by one study group [15]. Registry comparison across two large cooperative groups has examined survival following relapse in a combined population [16], which is the design best placed to overcome the small subgroup sizes that limit single-trial analyses.

Why some children relapse and others do not: Relapse risk is set largely by disease biology present at diagnosis, and the classification used to describe it has changed considerably over the period covered by these cohorts [19,20,21]. Cytogenetic and molecular subgroup assignment now drives first-line risk stratification, and a child relapsing from a favourable-risk group differs biologically from one relapsing after adverse-risk disease even when the remission durations are identical [12,20].

That matters for interpreting the timing effect. If early relapse is commoner in adverse-risk genotypes, then part of what remission duration measures is the underlying genetics rather than acquired resistance. None of the studies reviewed here reports outcome by remission duration within molecularly defined subgroups, so the two explanations cannot be separated from the published data [12,19].

What the child survives before relapse is reached: Salvage outcome is not determined solely by leukaemia. Children reaching relapse have already received six to nine months of intensive therapy, and the cumulative organ toxicity, particularly cardiac from anthracycline exposure, constrains what reinduction can safely deliver [3,4,22]. Treatment-related death in first-line therapy has fallen across successive protocol generations [5,6,7], and the survivors of that improvement include patients who would previously not have reached the relapse setting at all.

Infection during salvage is the immediate practical constraint. Reinduction produces prolonged neutropenia in a child whose mucosal barriers and immune reconstitution are already compromised [22,23], and prophylaxis trials conducted in first-line paediatric acute myeloid leukaemia apply directly [24,25]. Central venous access, in place throughout, remains an independent risk factor for bloodstream infection [26].

Group	Reported outcome	Implication
Late relapse, good day 28 response	55% at four years [13]	Best available; still nearly half die
Second remission achieved	47% at three years [10]	Proceed to transplant
Early relapse	38% at two years [1]	Intensive salvage still justified
Day 28 blasts above 20%	14% at four years [13]	Candidate for experimental therapy or palliation
No second remission	8% at three years [10]	Further intensification rarely helps

Table 3: Reported outcome by prognostic group after first relapse, with the management implication each carries

Discussion

Duration of first remission is a real prognostic factor. The international trial found two-year survival of 38 per cent after early relapse against 54 per cent after late relapse, and the wider literature reports the same direction with wider ranges [1,13]. Nothing here argues that the observation is wrong.

What the same data show is that it has been superseded. Marrow response at day 28 separates four-year survival from 14 to 52 per cent, more than twice the spread attributable to relapse timing, and it does so across four graded categories rather than two [13]. Achieving second remission separates three-year survival from 8 to 47 per cent [10]. Both measures outperform the one fixed before treatment starts.

Why the later measure is the more useful one

Remission duration is known at the moment of relapse and cannot change. That makes it convenient for counselling and useless for treatment decisions, because by the time it is available the decision it might inform has already been framed. Day 28 response arrives four weeks later, when the choice between proceeding to transplant, switching to an experimental agent, or moving to palliation is genuinely open [13].

This is the same logic that governs measurable residual disease in first-line therapy, where response to treatment displaced presenting features as the dominant prognostic variable [17,18]. Relapsed disease has been slower to adopt it, partly because relapse cohorts are small and partly because the timing categories are entrenched in trial eligibility.

What the numbers do not resolve

A four-year survival of 55 per cent in the most favourable group, late relapse with good early response, is the ceiling of what current salvage delivers [13]. For the least favourable group the figure is 14 per cent, and the investigators framed their analysis explicitly around identifying those patients as candidates for experimental therapy or palliation rather than further intensification [13].

That framing is unusual in paediatric oncology and worth noting. It concedes that for a definable subgroup, more of the same treatment is not expected to help, and it uses a prognostic measure to say so rather than to escalate. Whether families and clinicians act on such a prediction is a separate question from whether the prediction is accurate.

Study limitations

The limitations belong to the underlying literature. Relapsed paediatric acute myeloid leukaemia is uncommon, so even international trials accrue a few hundred patients and subgroup analyses rest on small numbers with wide standard errors [1,8,13]. The threshold dividing early from late relapse differs between studies at twelve or eighteen months, and the reference point differs between diagnosis and documented remission, so cohorts labelled the same way are not equivalent [8,13]. Day 28 response was assessed by morphology rather than by flow cytometry or molecular methods, which are more sensitive and now more widely available [13,18]. Transplantation was not randomly assigned in any cohort reviewed, so comparisons between post-remission strategies are confounded by selection [8,14]. And several formative series predate current cytogenetic and molecular classification, so the populations differ from those seen today [8,11,12].

Two gaps deserve naming. No study has tested prospectively whether assigning salvage intensity by day 28 response rather than by relapse timing improves outcome, although the comparative data imply it should [13]. And no analysis reviewed here reports outcome by remission duration within molecularly defined subgroups, so it remains unclear whether the timing effect reflects biology captured by current genetic classification or something additional to it [12,19].

Conclusion

Duration of first complete remission predicts outcome after relapse of childhood acute myeloid leukaemia, with two-year survival of 38 per cent for early and 54 per cent for late relapse in the largest international trial. It is nonetheless the weakest of the measures available. Achieving second remission separates three-year survival from 8 to 47 per cent, and marrow blast count at day 28 after the first reinduction course separates four-year survival from 14 to 52 per cent across four graded categories, with no equivalent signal at day 15. Remission duration is fixed before any decision is made; day 28

response arrives while the decision is still open. Even in the most favourable group, late relapse with good early response, four-year survival reaches only 55 per cent, which is the measure of how much room remains in salvage therapy for this disease.

Two changes would improve on this. Assessing day 28 response by flow cytometry or molecular methods rather than morphology would refine a measure already shown to work, since a morphological threshold of five per cent blasts is coarse relative to what current assays detect [13,18]. And reporting relapse outcome within molecularly defined subgroups would establish whether remission duration carries information beyond the genetics already known at diagnosis, which no study reviewed here can answer [12,19,20].

Until then, the practical position is straightforward. Remission duration remains worth knowing and worth explaining to families, but it should not be the variable that decides how a child is treated. The marrow at day 28 says more, and says it at a point when the answer can still change what happens next.

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Conflict of Interest

No relationship, commercial or academic, needs declaring here.

Ethics Statement

The whole of this was assembled from trials and registries already in print. No child was enrolled for it and no case note was reopened, so no ethics application was made.

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