SOMATO PUBLICATIONS ISSN: 2688-9587

Annals of Leukemia Research

Review Article

Central Nervous System Involvement at Diagnosis and Long-Term Outcomes in Paediatric Acute Lymphoblastic Leukemia

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Received: 06 January 2026; **Accepted:** 30 March 2026; **Published:** 11 July 2026

Citation of this article: Kovacic, A., Berzins, A., Hudakova, K. (2026) Central Nervous System Involvement at Diagnosis and Long-Term Outcomes in Paediatric Acute Lymphoblastic Leukemia. Ann Leuk Res, 7(1): 04-06. doi: 10.5281/zenodo.22247788

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Summary

Central nervous system status at diagnosis is assigned from a single cerebrospinal fluid sample and determines how intensively a child is treated. Two findings unsettle that arrangement: the borderline category carries no consistent prognostic weight, while a bloody tap, which is an event of the procedure rather than of the disease, consistently does.

Objectives: To review the published evidence on central nervous system involvement at diagnosis in paediatric acute lymphoblastic leukaemia: how status is classified, what each category predicts, why the studies disagree, what a traumatic tap contributes, and what long-term cost the associated therapy carries.

Material and Methods: Narrative review of cooperative group trial analyses, single-institution protocols, classification algorithms and late-effects studies indexed in PubMed and the major haematology and paediatric oncology journals. Studies were eligible if they reported the prognostic effect of central nervous system status at diagnosis, or the outcomes of central nervous system-directed therapy, in a defined paediatric acute lymphoblastic leukaemia population. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: In a cohort of 2,021 children, overt central nervous system disease carried a risk ratio for treatment failure of 2.3 (95% CI 1.4-3.6, $p = 0.0005$) and traumatic lumbar puncture with blasts a ratio of 1.5 (95% CI 1.02-2.2, $p = 0.04$), while the borderline CNS2 category was not independently significant. A separate trial found event-free survival of 72.6, 70.3 and 66.7 per cent across CNS1, CNS2 and CNS3 with no significant difference between them, against 58 per cent for traumatic tap with blasts and 82 per cent without ($p < 0.01$), and identified traumatic tap as an independent factor with a risk ratio of 3.5 (95% CI 1.4-8.8, $p = 0.007$). A protocol omitting cranial irradiation entirely reported five-year event-free survival of 80.8 per cent with isolated central nervous system relapse in 1.7 per cent and isolated plus combined relapse in 3.0 per cent. Where all patients with any central nervous system finding received intensified intrathecal therapy, status ceased to predict relapse.

Conclusion: The category that predicts most reliably is produced by the diagnostic procedure rather than by the leukaemia, which makes it modifiable in a way the disease is not. Where intensified therapy is given to all patients with any finding, the prognostic effect disappears.

Abbreviations: ALL – Acute Lymphoblastic Leukaemia, CNS – Central Nervous System, CSF – Cerebrospinal Fluid, CNSL – Central Nervous System Leukaemia, TLP – Traumatic Lumbar Puncture, LP – Lumbar Puncture, IT – Intrathecal, MTX – Methotrexate, WBC – White Blood Cell, RBC – Red Blood Cell, EFS – Event-Free Survival, RR – Risk Ratio, Gy – Gray.

Keywords: *Acute Lymphoblastic Leukaemia; Central Nervous System; Traumatic Lumbar Puncture; Cranial Irradiation; Paediatric Oncology*

Introduction

The central nervous system is a sanctuary site in acute lymphoblastic leukaemia, and before directed prophylaxis was introduced the majority of children relapsed there [1,2]. Contemporary protocols have reduced isolated central nervous system relapse to a few per cent, which is among the clearest successes in paediatric oncology [3,4].

Status at diagnosis is assigned from a single cerebrospinal fluid sample taken at the first lumbar puncture. The conventional scheme distinguishes CNS1, with no blasts; CNS2, with five or fewer white cells per microlitre but identifiable blasts; and CNS3, with more than five

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white cells and blasts, or clinical signs such as cranial nerve palsy, intracranial mass, retinal involvement or hypothalamic syndrome [5,6].

Where the tap is traumatic, the picture is confounded. Circulating blasts from peripheral blood can contaminate the specimen, and an algorithm comparing the cerebrospinal fluid white-to-red cell ratio against the blood ratio is used to decide whether genuine involvement is present [6,7]. A traumatic tap with blasts has itself been shown to carry prognostic weight [8].

This review sets out what each category predicts, why cooperative groups have reached different conclusions, what the procedural finding contributes, and what the therapy given in response costs over a lifetime.

Material and Methods

Search strategy: PubMed and the archives of the major haematology and paediatric oncology journals were searched for studies of central nervous system involvement in childhood leukaemia. Search terms combined acute lymphoblastic leukaemia and paediatric with central nervous system status, CNS2, CNS3, traumatic lumbar puncture, intrathecal therapy, cranial irradiation and neurocognitive outcome. Reference lists of retrieved trial analyses were screened by hand.

Eligibility: Studies were included if they reported the prognostic effect of central nervous system status at diagnosis or the outcomes of directed therapy in a defined paediatric acute lymphoblastic leukaemia population. Studies in myeloid leukaemia are cited where they illustrate the same classification difficulty and are identified as such.

Data extraction and handling: Cohort size, classification criteria, the treatment assigned to each category and reported outcome estimates were extracted as published. The treatment assigned to each category is stated alongside every outcome, because most cohorts intensified therapy for the categories they were assessing, which is the principal reason reported prognostic effects differ between studies. 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

What the largest cohort found: Cerebrospinal fluid from 2,021 children enrolled in a cooperative group trial was evaluated retrospectively, classifying 1,605 as CNS1, 103 as CNS2, 58 as CNS3, 135 as traumatic tap with blasts and 111 as traumatic tap without blasts [8]. Patients with CNS2 or traumatic tap with blasts received two additional doses of intrathecal methotrexate; CNS3 patients received additional intrathecal therapy and 18 Gy cranial irradiation [8].

Cox regression identified two categories as prognostically significant: CNS3 with a risk ratio of 2.3 (95% CI 1.4 to 3.6, p = 0.0005) and traumatic tap with blasts at 1.5 (95% CI 1.02 to 2.2, p = 0.04) (Figure 1) [8]. CNS2 did not reach independent significance, although the CNS2, CNS3 and traumatic tap groups all contained a higher proportion of patients with otherwise unfavourable characteristics [8].

That last observation matters for interpretation. If the categories are enriched for high presenting white cell count, T-lineage disease and adverse genetics [8,9], then part of any apparent prognostic effect reflects those features rather than the central nervous system finding itself.

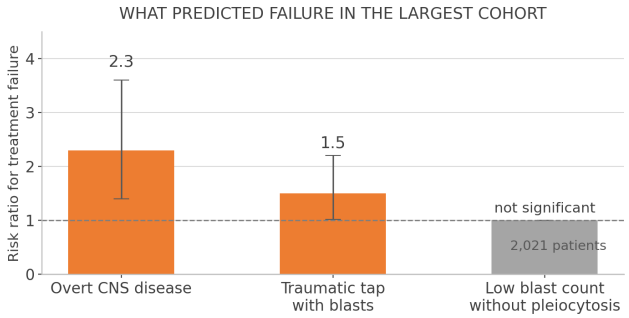

Figure 1: Risk ratios for treatment failure by cerebrospinal fluid category in 2,021 children [8]

The borderline category does not hold up: A separate cooperative group trial reported event-free survival of 72.6 per cent (SE 2.5) for CNS1 patients, 70.3 per cent (SE 4.7) for CNS2 and 66.7 per cent (SE 19) for CNS3, with no significant difference between the groups [10]. Cumulative incidence of central nervous system relapse was 0.05 in CNS1 and 0.07 in CNS2, again not significantly different [10].

The same analysis found event-free survival of 58 per cent (SE 7.6) for traumatic tap with blasts against 82 per cent (SE 5.2) without ($p < 0.01$), and Cox regression identified traumatic tap with blasts as an independent prognostic factor with a risk ratio of 3.5 (95% CI 1.4 to 8.8, p = 0.007) (Figure 2) [10]. The investigators concluded that a low number of blasts without pleiocytosis has no prognostic significance, while a traumatic tap with blasts is associated with inferior outcome [10].

Not all groups agree. Analysis from another cooperative group found central nervous system leukaemia at diagnosis associated with worse three-year event-free survival (p = 0.030) and higher cumulative relapse (p = 0.008), with a multivariate hazard ratio of 2.809 (p = 0.016), though with no effect on overall survival (p = 0.837) [11]. Reviews have noted explicitly that not all studies confirm a negative prognostic impact of CNS2 status [12].

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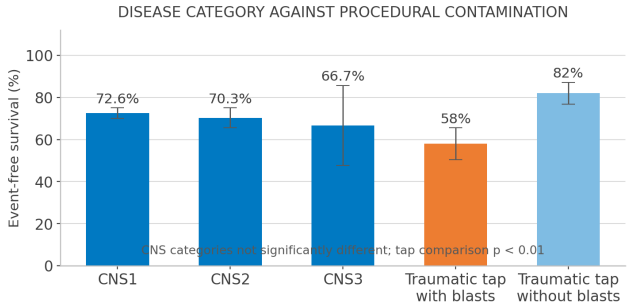

Figure 2: Event-free survival by category in a trial treating without cranial irradiation [10]

Study	n	Treatment of category	Principal reported finding
Bürger et al. 2003 [8]	2,021	Extra intrathecal; irradiation for CNS3	CNS3 and traumatic tap significant; CNS2 not
Gajjar et al. 2000 [13]	—	Intensified for contaminated tap	Blast contamination adversely affects outcome
EORTC 58951 [10]	—	No cranial irradiation	Traumatic tap independent; CNS categories not
Pui et al. 2009 [3]	498	Irradiation omitted entirely	Isolated CNS relapse 1.7 per cent
Jeha et al. 2021 [14]	Cohort	Intensified for any CNS finding	CNS status ceased to predict relapse
South China group [11]	Cohort	Two extra intrathecal courses	CNS leukaemia adverse, hazard ratio 2.809

Table 1: Principal studies reviewed, with the treatment each category received and the finding as reported

Why a bloody tap matters: The mechanism is contamination. Leukaemic cells circulating in peripheral blood enter the cerebrospinal fluid specimen during a traumatic puncture, and those cells can seed the compartment as well as appear in it [7,13]. Contamination of cerebrospinal fluid with circulating blasts during diagnostic lumbar puncture adversely affects treatment outcome and is an indication to intensify intrathecal therapy [13].

There is a second mechanism operating in the same direction. Blood in the space can impair the efficacy of subsequent intrathecal treatment through haematoma or scarring, and can mask the presence of genuine CNS2 or CNS3 disease on that first sample [7]. A traumatic tap therefore both creates risk and degrades the measurement used to assess it.

Because the event is procedural, it is preventable. Recommendations to avoid traumatic puncture include performing the diagnostic procedure under general anaesthesia and by an experienced operator, and to defer it where the circulating blast count is very high [12,15]. No other adverse prognostic factor in this disease is modifiable by technique.

What happens when everyone is treated: A single-institution protocol omitting cranial irradiation entirely reported five-year event-free survival of 80.8 per cent (SE 2.6) and eight-year survival of 78.6 per cent (SE 5.8), with five-year cumulative risk of isolated central nervous system relapse of 1.7 per cent (SE 0.8) and of isolated plus combined relapse of 3.0 per cent (SE 1.1) (Figure 3) [3].

Its successor protocol intensified early intrathecal therapy for every patient with any central nervous system involvement, including CNS2, CNS3 and traumatic tap with blasts, alongside other risk features [14]. In that cohort, CNS2, CNS3 and traumatic lumbar puncture were not associated with the risk of central nervous system relapse, and 1.3 per cent nonetheless experienced isolated relapse [14].

A prognostic factor that stops predicting when acted upon is the expected result of effective treatment, not a refutation of the original observation. It does mean that studies reporting no effect of CNS2 cannot be read as evidence that CNS2 is harmless, because those patients received additional therapy [8,10,14].

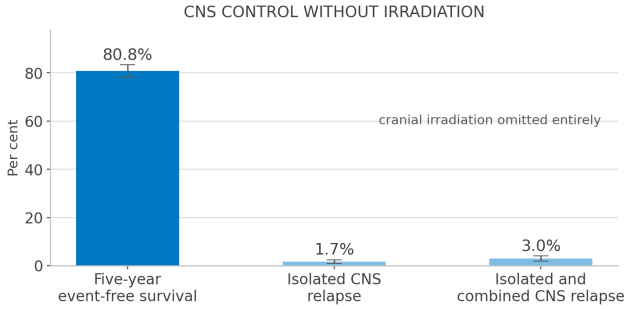

Figure 3: Central nervous system control in a protocol omitting cranial irradiation [3]

What the prophylaxis costs: Cranial irradiation at 12 to 18 Gy is given to between 2 and 20 per cent of patients with lymphoblastic leukaemia judged at increased risk of central nervous system relapse, including those with T-lineage immunophenotype, overt disease, high-risk cytogenetics or poor induction response, and this restricts relapse to between 3 and 8 per cent (Figure 4) [15].

The long-term cost falls on survivors. Neurocognitive impairment, endocrine dysfunction and second malignancy following cranial irradiation are the principal reasons protocols have moved away from it [16,17,18], and contemporary approaches achieve comparable control with intrathecal therapy alone [3,19].

Removing irradiation does not remove the cost entirely. Increased exposure to and duration of total intravenous anaesthesia for additional intrathecal treatments may itself affect neurocognitive

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function [14,20]. The intensification given to protect a minority is delivered under anaesthesia to a much larger group.

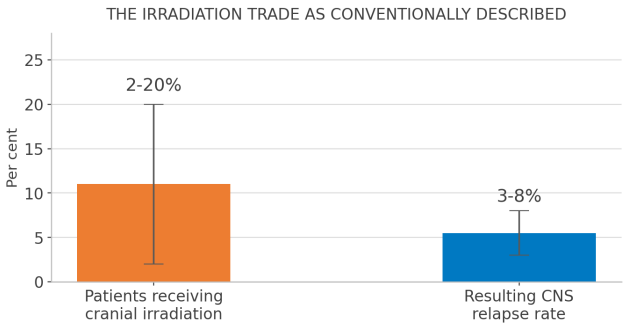

Figure 4: Proportion irradiated and the resulting relapse rate as conventionally described [15]

Category	Definition	Reported prognostic effect
CNS1	No blasts in cerebrospinal fluid	Reference [5,8]
CNS2	Five or fewer cells per microlitre with blasts	Inconsistent; often absent [8,10,12]
CNS3	Over five cells with blasts, or clinical signs	Adverse, risk ratio 2.3 [8]
Traumatic tap with blasts	Blood-contaminated specimen containing blasts	Adverse, risk ratio 1.5 to 3.5 [8,10]
Traumatic tap without blasts	Blood-contaminated, no blasts	Not adverse [8,10]

Table 2: Classification categories and what each has been reported to predict

What a more sensitive assay would change: Morphological examination of a cytospin is the least sensitive method available for detecting leukaemic cells, and flow cytometric detection of blasts in cerebrospinal fluid predicts relapse risk in cohorts where morphology found nothing [26]. That raises the possibility that CNS1 as currently defined contains patients with occult involvement.

If so, the inconsistent behaviour of CNS2 has a further explanation: the comparator group is contaminated. A reference category that includes undetected disease will narrow any apparent difference, which is what the event-free survival figures of 70.3 against 72.6 per cent look like [10,26]. Clinical features and early treatment response in patients with confirmed involvement have been described separately [23].

Larger cooperative group analyses have examined the impact of initial cerebrospinal fluid findings on outcome across standard and high-risk populations [25], and imaging findings at presentation have been characterised where clinical involvement is suspected [27]. Neither resolves the sensitivity question, which requires the assay to change rather than the cohort to enlarge.

Where central nervous system status sits among modern risk factors: Response to treatment measured as minimal residual disease has displaced most presenting features in this disease [21,22], and protocols now reduce or intensify therapy on that basis with demonstrated safety [28,29]. Central nervous system status is one of the few presenting characteristics that continues to modify treatment independently of response [14,30].

Its persistence is justified by compartment rather than by prognosis. Marrow residual disease measurement says nothing about the cerebrospinal space, so a child who clears the marrow completely may still harbour disease where the assay does not look [22,26]. That is a coherent reason to retain the classification even where its prognostic effect under treatment is small.

Element	Current practice	What the evidence supports
Detection method	Morphology on cytospin	Flow cytometry predicts relapse where morphology does not [26]
CNS2 management	Two extra intrathecal doses	Effective; necessity untested [8,10]
Traumatic tap prevention	Anaesthesia, experienced operator	The one modifiable adverse factor [12,13]
Cranial irradiation	Largely abandoned	Comparable control without it [3,19]

Table 3: Elements of current practice and the evidence behind each

Discussion

The finding that deserves most attention is that the most reproducible adverse category in this classification is not a property of the leukaemia. Traumatic tap with blasts predicted failure in both large cohorts reviewed, at risk ratios of 1.5 and 3.5 [8,10], while the borderline disease category CNS2 reached significance in neither [8,10].

That inverts the usual relationship between marker and modifiability. A child's cytogenetics, presenting count and lineage cannot be altered; the quality of their first lumbar puncture can [12,13,15]. An adverse prognostic factor created by the diagnostic process is one that better technique could remove entirely.

Why the studies disagree about CNS2

The disagreement is largely explicable by treatment. In the cohorts reporting no effect of CNS2, those patients received additional intrathecal methotrexate precisely because they were CNS2 [8,10], and in the protocol intensifying therapy for any central nervous system finding, status ceased to predict relapse altogether [14].

A null result under treatment is not the same as absence of risk. The correct inference is that CNS2 identifies patients whose risk is

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abolished by two extra intrathecal doses, which is a useful thing to know and a different claim from the category being prognostically inert [8,10,14]. Studies reporting an adverse effect used less intensive augmentation [11].

The cost of protecting a minority

Isolated central nervous system relapse now occurs in around 1.7 per cent of children treated without irradiation [3], and 1.3 per cent even under intensified intrathecal therapy [14]. The prophylaxis preventing those events is delivered to every patient, and where irradiation is used it reaches 2 to 20 per cent [15].

The relevant harms have shifted rather than disappeared. Irradiation carries neurocognitive, endocrine and second malignancy risk [16,17,18]; its replacement carries repeated general anaesthesia, which may itself affect neurocognitive outcome [14,20]. Both costs fall on the large majority who would never have relapsed in the compartment.

Study limitations

The limitations belong to the underlying literature. Every cohort intensified therapy for the categories it was assessing, so reported prognostic effects are effects under treatment rather than natural history [8,10,14]. Category sizes are small, with CNS3 numbering 58 in one cohort and 10 in another, giving standard errors as wide as 19 per cent [8,10]. Classification criteria differ, with some groups applying the cell-ratio algorithm and others not [6,7,11]. Adverse categories are enriched for other unfavourable features, so residual confounding is substantial [8,9]. And rates of traumatic puncture depend on operator experience and on whether anaesthesia is used, which differ between centres and eras and are seldom reported [12,15]. And the burden of intensified therapy extends beyond the nervous system to complications such as corticosteroid-related osteonecrosis and to differences in maintenance tolerability, which are seldom counted alongside neurocognitive outcome [24,31,32].

Two gaps deserve naming. No trial has randomised the intensity of intrathecal therapy by CNS2 status, so whether those two extra doses are necessary is unestablished [8,10]. And no study reviewed here reports neurocognitive outcomes stratified by the number of intrathecal procedures received, which is what would quantify the cost of the current approach [14,20].

Conclusion

Central nervous system status at diagnosis assigns children to more intensive therapy on the basis of a single cerebrospinal fluid sample. Overt disease carries a risk ratio for failure of 2.3, and the borderline CNS2 category reached independent significance in neither of the two large cohorts reviewed, with event-free survival of 70.3 against 72.6 per cent for CNS1 in one of them. Traumatic lumbar puncture with blasts predicted failure in both, at 1.5 and 3.5, and it is an event of the procedure rather than of the leukaemia, making it the one adverse factor in this disease that better technique could remove. Where all patients with any central nervous system finding received intensified intrathecal therapy, status ceased to predict relapse at all, which shows the treatment works and means null results cannot be read as evidence of absent risk. Isolated relapse now runs at 1.7 per cent without cranial irradiation, and the prophylaxis preventing it is borne by everyone.

Acknowledgements

The authors thank the cooperative study groups whose published trial analyses form the substance of this article.

Funding

No dedicated funding from public, commercial or charitable sources supported this review.

Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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