



ORIGINAL ARTICLE

High need for intensive care in paediatric acute myeloid leukaemia: A population-based study

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Abstract

Aim: Risk of treatment-related life-threatening toxicity is high in childhood acute myeloid leukaemia (AML), and access to intensive care units (ICU) is crucial. We explored the ICU admission rate and outcome after intensive care in childhood AML in Sweden.

Methods: Patients diagnosed between 2008 and 2016 were identified from the Swedish Childhood Cancer Registry (SCCR), a national quality registry. Data from SCCR was cross-referenced with clinical questionnaire data from paediatric oncology centers and the Swedish Intensive Care Registry (SIR), another national quality registry.

Results: According to combined data, 46% of the children (58/126) were admitted to ICU, 17% (21/126) within 1 month from diagnosis. Overall, ICU mortality per admission was 12% and 6% during first-line treatment. There was a discrepancy between admission rate from the clinical questionnaires and SCCR (29%; 36/126 children) and SIR (44%; 55/126). All deaths during first-line treatment occurred at or after ICU care.

Conclusion: Although admission rate under AML treatment was high, the treatment-related mortality under first-line treatment was low. No child died under first-line treatment without admission to ICU, suggesting good availability. The discrepancy between the two registries, SCCR and SIR, highlights the need for future validation of registry data.

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; HR, high risk; ICU, intensive care unit; IQR, interquartile range; SPSS, statistical package for the social sciences; SCT, stem cell transplantation; SCCR, Swedish Childhood Cancer Registry; SIR, Swedish Intensive Care Registry.

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KEYWORDS

AML, children, incidence, intensive care

1 | INTRODUCTION

The outcome for paediatric acute myeloid leukaemia (AML) has improved in recent decades. This success is due to intensified treatment strategies, better supportive care, and international collaboration to develop risk-adapted treatment.^{1–3} Yet, approximately 30% of patients relapse.⁴ Moreover, as the therapy is based on intensive heavily myelosuppressive chemotherapy, 5%–10% die of treatment-related toxicity, mainly infections.^{5–7} The availability and criteria for intensive care varies between countries and even between treatment centers. Malignancy, in particularly AML, was previously considered a relative contraindication for intensive care and children with malignancies in intensive care have higher mortality rate compared to other children, which may influence the attitude of the caregiver and thus their access to intensive care.^{8,9} In Sweden, only patients requiring continuous observation and support for vital organ functions are admitted to the intensive care unit (ICU). The aim of this study was to explore the need for and access to intensive care in paediatric AML in Sweden, as well as long-term outcome after ICU admission.

2 | METHODS

2.1 | The study cohort and data sources

Children <18 years at diagnosis of myeloid malignancy between 2008 and 2016 in Sweden were identified from the national quality registry, the Swedish Childhood Cancer Registry (SCCR). Only AML patients were included, while children with myelodysplastic syndrome, Down syndrome, transient acute myeloid disorder or missing data were excluded. The treatment of de-novo AML was based on two NOPHO AML protocols (From January 2008 to January 2013 NOPHO AML2004,^{1,10} thereafter NOPHO-DBH AML2012 [EUdract number 2012-002934-35]). High-risk (HR) group, determined by poor response to treatment after first or second courses or unfavourable cytogenetics, was eligible to allogeneic stem cell transplantation (SCT) in first remission in both protocols. Also, children with acute promyelocytic leukaemia, mixed-phenotype acute leukaemia, or juvenile myelomonocytic leukaemia were excluded as their therapy differs from standard AML treatment.

Data retrieved from the SCCR included clinical characteristics, details on AML treatment, outcome and, from February 2013 onwards, ICU admissions under AML treatment. All Swedish paediatric treatment centers were asked to complete a short questionnaire on those with registered ICU admission in SCCR. As intensive care admissions under AML treatment were not registered in the SCCR prior to February 2013 when the NOPHO-DBH AML2012 was introduced, the centers reviewed all charts of patients with AML diagnosed between January 2008 and January 2013. For patients diagnosed from February 2013 onwards, chart review was only performed for patients

Key Notes

- Combined data from two national quality registries, the Swedish Childhood Cancer Registry (SCCR) and the Swedish Intensive Care Registry (SIR), demonstrated that 46% of children with acute myeloid leukaemia are admitted to intensive care unit (ICU), with SIR having more registered admissions than SCCR.
- Infections were the most common reason for admission.
- Treatment-related ICU mortality during first-line AML treatment was low (2% (or 1/65)).

with registered intensive care in the SCCR. A short questionnaire was completed separately on each identified intensive care admission. The questionnaire covered the main indication for admission to the ICU, time in the ICU (in days), presence of neutropenia, positive blood cultures, and the need for mechanical ventilation or inotropes. The questionnaire data were then combined with data from the SCCR.

Simultaneously, a list of all study patients from the SCCR was submitted to the Swedish Intensive Care Registry (SIR), for cross-referencing. Data from SIR included route and time of day of admission and discharge, main diagnosis, and outcome (dead or alive) at and up to 30 days from discharge. Data from SIR was combined with the database containing data from SCCR and the questionnaires.

The data set was anonymised when the data from different sources were combined by SCCR; therefore, it was not possible to send the treatment centers queries on patients identified in the SIR but missing questionnaires. See Table S1 for data sources for the different variables.

Intensive care units admissions were considered a single admission if the patient was not discharged to a hospital ward between admissions. Admissions starting 10 days before AML diagnosis were included. If the time of day of admission or discharge was missing, the timepoint was marked as 12:00 ($n = 4$). If time for both admission and discharge during the same day were missing, the ICU stay was recorded as 6 h ($n = 1$). ICU mortality was calculated by deaths per admissions. De novo AML treatment before relapse or SCT were considered first-line treatment.

2.2 | Statistics

Patient characteristics were summarised by descriptive statistics. Categorical data is presented as numbers and fractions (%), and continuous data are presented as medians (Interquartile range [IQR] 25%–75%). Categorical group differences were assessed by Chi-square or Fisher's exact test and continuous by using the Mann-Whitney U test. Five-year overall survival (OS), defined as days from

diagnosis until death from any cause, was estimated using survival analysis by Kaplan–Meier. A two-sided p -value < 0.05 was considered statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 25 for Windows.

This study was approved by the Regional Ethics Review Board in Stockholm (2017/1721-31/1).

3 | RESULTS

3.1 | The study cohort

Of the 172 patients in the SCCR with any myeloid malignancies diagnosed in 2008–2016, 126 fulfilled the inclusion criteria, eight with secondary AML (Figure 1), 72 of whom were diagnosed under NOPHO AML2004 and 54 NOPHO-DBH AML2012 protocol period. Demographic and clinical data on AML were available for all patients from the primary source (SCCR). When all data sources were utilised, 94 ICU admissions were reported for 58 children. Twenty-one of those occurred in 12 children after SCT corresponding to 21% of all transplanted patients. There was no significant difference in ICU admission between the two protocol periods ($p = 0.502$). SIR

covered 95% of the identified patients with intensive care, and 95% of all admissions (55/58 and 89/94, respectively). Questionnaires were returned for 64% (36/58) of the patients and 56% (53/94) of all ICU admissions. The questionnaire return rate from the clinics did not differ between patients diagnosed before February 2013 and more recently. However, all patient files were reviewed in the earlier period, whereas in the latter only patients registered in the SCCR were reviewed. Questionnaires were returned from 21/35 patients diagnosed before and 15/23 after, $p = 0.785$. Two patients with questionnaire data diagnosed after February 2013 were not registered in SCCR as the intensive care occurred before the treatment start. ICU data from all three sources were available in 57% (33/58) of patients and 51% (48/94) of admissions.

There were no significant differences in characteristics between patients with and without admission to ICU (Table 1).

3.2 | Intensive care periods

Ten percent of children (13/126) required intensive care shortly before or on the day of diagnosis, and 17% (21/126) before the end of the first month. The main causes for ICU admission are shown in Figure 2. Admission and discharge routes are shown in Table S2.

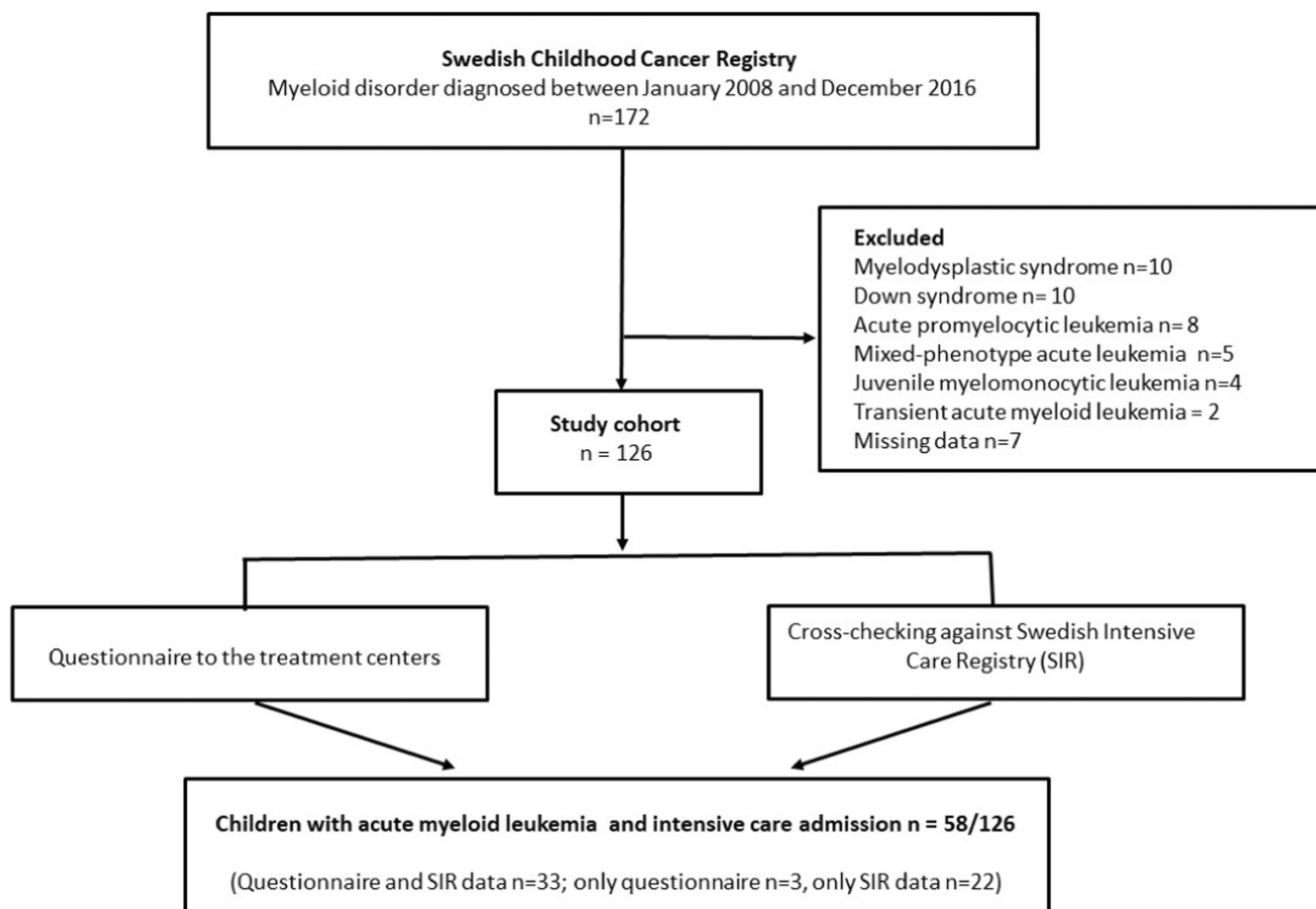


FIGURE 1 Flow chart illustrating data gathering from the three sources: Swedish Childhood Cancer Registry, patient charts, and the Swedish Intensive Care Registry

TABLE 1 Clinical characteristics of 126 children with acute myeloid leukaemia (AML) with and without intensive care admission

	ICU admission (n = 58)	No ICU admission (n = 68)	p
Age in years, median [IQR]	9.3 [2.3–15.0]	6.2 [2.4–13.1]	0.378
<10 years (%)	31 (53)	44 (65)	0.209
≥10 years (%)	27 (47)	24 (35)	
Gender (%)			
Male	34 (59)	37 (54)	0.719
Female	24 (41)	31 (46)	
Median WBC at diagnosis [IQR] ^a	24.0 [7.3–54.5]	29.0 [8.5–74.2]	0.388
Initial CNS involvement ^b			
Yes	2 (4)	6 (9)	0.463
No	49 (96)	60 (91)	
Missing data	7	2	
SCT at any time (%)	27 (47)	29 (43)	0.721
Primary events (%)			
Induction death	1 (1.5)	1 (1.3)	0.491
Resistant disease	3 (4)	1 (1.3)	
Relapse	15 (22)	15 (19)	
Death in first complete remission	2 (3)	0	
SMN	1 (1.5)	0	
Risk group			
SR	40	49	0.823 ^b
HR	12	13	
Non-protocol/early death/other	2/2/2	5/0/1	

Abbreviations: CNS, central nervous system; HR, high-risk; ICU, intensive care unit; IQR, interquartile range; SCT, stem cell transplantation; SMN, secondary malignant neoplasm; SR, standard risk; WBC, white blood cell count.

^aHighest WBC at diagnosis. Data missing from one patient with ICU admission.

^bOnly patients with known CNS involvement or risk group were compared.

3.3 | Survival after intensive care

Five-year overall OS from the AML diagnosis was 61% in children with and 79% without intensive care. Overall, 36% (21/58) of children with and 19% (13/68) without ICU admissions were deceased at the end of follow-up.

Eleven children (6/35 before and 4/22 after February 2013 when the protocol period changed [$p = 0.271$]; one prior to AML treatment) died in the ICU (four under first-line treatment, two after relapse without SCT and five after SCT) and another eight within 30 days after discharge. ICU mortality was 12% (11/94 admissions); 8% (6/73) before and 24% (5/21) after SCT and 15% (11/73) and 38% (8/21), respectively, for 30-day mortality. No child died without

being admitted to ICU during first-line treatment. Three of the deaths during first-line treatment were directly related to the underlying leukaemia and one to therapy-related toxicity. ICU mortality per admission before or under first-line treatment was 6% (4/65 admissions in 42 children including one patient who died 3 days after transfer to another ICU).

Of the eight patients with AML as a secondary malignancy, six had died. Half of them ($n = 4$) were admitted to ICU; of those, three were admitted after SCT and deceased. Three patients not admitted to ICU had died at time of follow-up.

3.4 | Comparison of data sources

Patients with completed clinical questionnaires ($n = 36$) were younger than those without ($n = 22$), median age 6.0 (IQR 0.9–14.4) and 10.8 (6.0–15.9) years, respectively ($p = 0.032$). The ICU stay was longer for admissions with questionnaire data compared to those without (69 (19–155) vs. 17 (1–70) hours, respectively, $p < 0.01$). Also, the questionnaire of the first admission was more often missing with longer time after the AML diagnosis (days to first admission from diagnosis with and without questionnaire data, 38 (0–96) and 164 (41–442), $p < 0.01$). The main reason for admission was observation in 13% (7/53) of those with, and 38% (11/29, missing data $n = 12$) without, questionnaire data. There were no differences in the number of admissions from the surgery, of sex, white blood cell count at diagnosis, central nervous system involvement, or risk group between patients with questionnaire data and those without.

3.5 | Cohort identified from the patient charts

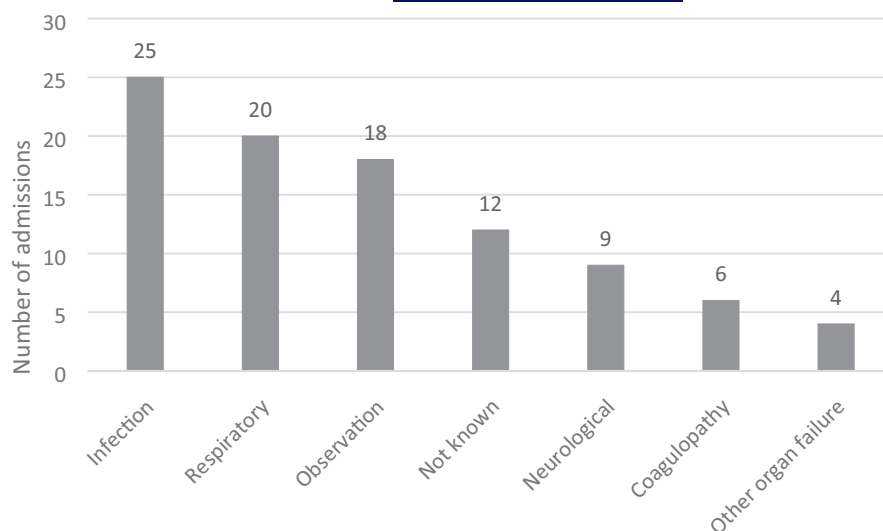
When only patients identified by the chart review were considered, 29% (36/126 children with 53 admissions) had been admitted to ICU at least once. ICU mortality per admission was 13% (7/53 admissions and 8/36 children, questionnaire from the last admission missing from one patient). ICU mortality under first-line treatment was 10% (4/42 admissions) and 5-year OS from the AML diagnosis was 65%. Overall, 33% (12/36) of children with were dead at the end of follow-up.

Comparison of ICU survival based on questionnaire data of 53 intensive care admissions for 36 patients showed that ventilator and inotropic agents were more frequently used in those who died in ICU, while neutropenia, invasive fungal infection or positive blood culture were not associated with worse ICU survival. (Table 2).

4 | DISCUSSION

Treatment of childhood AML is based on intensive myelosuppressive chemotherapy with high risk for life-threatening toxicity and novel approaches are being investigated especially for relapsed or refractory AML.^{2,11} This national population-based registry study confirms the high rate of ICU admissions in children with AML in

FIGURE 2 Main reasons for admission to intensive care. Data missing for 12 patients



Data missing for 12 patients

TABLE 2 Data on chart review of 53 intensive care periods of 36 children with AML

	Survived the ICU period <i>n</i> = 47 admissions	Died at ICU <i>n</i> = 7 admissions ^a	<i>p</i> -Value ^b
Any severe infection			
Yes	32	6	1.000
No	12	0	
Missing data	2 (2 not relevant)	1 (suspected IFD)	
Neutropenia (<0.5 × 10 ⁹ /L)			
Yes	18	2	0.016
No	4	5	
Missing data	24 (2 not relevant)		
Positive blood culture			
Yes	20	1	0.095
No	16	5	
Missing data	10 (2 other major infection, 8 not suspected)	1	
Invasive fungal infection			
Yes	9	2	1.000
No	34	3	
Missing data	3 (2 suspected, 1 not relevant)	2 (1 suspected)	
Kidney failure and dialysis			
Yes	2	2	0.061
No	44	4	
Missing data		1	
Mechanical ventilation			
Yes	9	6	0.001
No	36	1	
Missing data	1		
Inotropic agents			
Yes	3	3	0.017
No	43	3	
Missing data		1	

Note: Bold indicates statistically significant *p*-values.

^aQuestionnaire data missing from the last admission of one patient.

^b*p*-values were analysed using Fisher's exact test without missing data.

Sweden; almost half of the whole cohort had received intensive care. However, another important finding is a discrepancy in reported admission rates between data from the paediatric oncology treatment centers (29%) and SIR (44%).

Admissions not identified by chart review and lacking questionnaire data were shorter, occurred later after the AML diagnosis and were more often attributed to observational character than those with questionnaire data, suggesting missing notes in patient charts for short observations, possibly partly due to separate journal system used by ICUs or intensive care outside university hospitals. Our study in children with acute lymphoblastic leukaemia (ALL) showed a similar discrepancy in registration.¹² This finding of discrepancy highlights the importance of data source in studies on ICU care. Validation by comparison between registry data and clinical records for both registries, as performed for other registries,^{13,14} could shed light on the differences in reporting.

Previous publication on NOPHO AML2004 including only protocol patients surviving the first induction course showed a lower ICU admission rate (19%) compared to our data, where all AML patients were included and identified by both chart review and SIR.⁷ In line with our work, an Australian study on 56 children with AML showed a high ICU admission rate (30%) and an ICU mortality of 25% due to sepsis and multi-organ failure.¹⁵ In our cohort, ICU mortality was 12% (6% during first-line treatment), and treatment-related mortality at ICU during first-line treatment was low with most early deaths being mainly related to the underlying disease. Also, no child with de novo AML died during first-line treatment without intensive care, suggesting good ICU availability. However, we lack data on the lag time, i.e., time from severe symptoms to ICU admission, which is also a measure of availability, and may affect outcome. A large cohort study from the United States comprising 1673 children treated for de novo AML prior to SCT showed an ICU admission rate of 33% and hospital mortality of 16% for admissions between 2004 and 2010.¹⁶ In their study, age above 10 years was a risk factor for ICU admission. We did not identify clinical risk factors associated with higher risk for ICU admission, probably due to our relatively small study cohort. Considering that the American study also included relapse treatment before SCT, mortality in our current study during first-line treatment was comparable to their results. Differences between registries, as shown in our study, and the patient cohorts make comparison of need and outcome of intensive care in childhood AML challenging.

The strengths of this study were the homogenous population-based cohort and good coverage of ICU admissions by combining two national quality registries with long-term follow-up. The main limitation was the relatively small cohort with comprehensive data from the questionnaires preventing confident conclusions. Also, data for the whole was combined from the two registries covering different levels of intensive care, with SIR being more inclusive. Further, no details on for example reasons for admission or type of operations for admission or interventions were available where only SIR data were available; we are unable to collect more information

on these admissions missing clinical questionnaires as the dataset was anonymized.

In conclusion, almost half of children with AML required intensive care, especially during early treatment. Infections were the most common reason for admission. ICU mortality associated with toxicity during first-line treatment of de novo AML was low. Our results highlight the different coverage between the two national quality registries, high need of intensive care during AML treatment, the good ICU outcome under first-line treatment and finally, the need for alternative less toxic treatment approaches.

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CONFLICT OF INTEREST

LMB: Medical Advisory Boards of Eurosets Srl., Medolla, Italy, and Xenios AG, Heilbronn, Germany. SR: Investigator in clinical trials promoted by Novo Nordisk, Roche and Sobi; Steering Committee for Roche. None of these engagements have influenced the current work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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