ICU Admission in Children With Acute Lymphoblastic Leukemia in Sweden: Prevalence, Outcome, and Risk Factors

Susanna Ranta, MD, PhD[1,2]
Lars Mikael Broman, MD, PhD[3,4]
Jonas Abrahamsson, MD, Prof[5]
Jonas Berner, MD, PhD[3,4]
Urban Fläring, MD, PhD[3,4]
Ida Hed Myrberg, MMath[1]
Håkan Kalzén, MD, PhD[6,7]
Lene Karlsson, MD
Karin Mellgren, MD, PhD[5]
Anna Nilsson, MD, PhD[1,2]
Ulrika Norén-Nyström, MD, PhD[8]
Josefine Palle, MD, PhD[9]
Katarina von Schewelov, MD, PhD[3]
Johan E. Svahn, MD, PhD[10]
Lisa Törnudd, MD[11]
Mats Heyman, MD, PhD[1]
Arja Harila-Saari, MD, Prof[9]

OBJECTIVES: Despite progress in the treatment of childhood acute lymphoblastic leukemia, severe complications are common, and the need of supportive care is high. We explored the cumulative prevalence, clinical risk factors, and outcomes of children with acute lymphoblastic leukemia, on first-line leukemia treatment in the ICUs in Sweden.

DESIGN: A nationwide prospective register and retrospective chart review study.

SETTING: Children with acute lymphoblastic leukemia were identified,and demographic and clinical data were obtained from the Swedish Childhood Cancer Registry. Data on intensive care were collected from the Swedish Intensive Care Registry. Data on patients with registered ICU admission in the Swedish Childhood Cancer Registry were supplemented through questionnaires to the pediatric oncology centers.

PATIENTS: All 637 children 0–17.9 years old with acute lymphoblastic leukemia diagnosed between June 2008 and December 2016 in Sweden were included.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Twenty-eight percent of the children (178/637) were admitted to an ICU at least once. The Swedish Intensive Care Registry data were available for 96% of admissions (241/252). An ICU admission was associated with poor overall survival (hazard ratio, 3.25; 95% CI, 1.97–5.36; $p \leq 0.0001$). ICU admissions occurred often during early treatment; 48% (85/178) were admitted to the ICU before the end of the first month of acute lymphoblastic leukemia treatment (induction therapy). Children with T-cell acute lymphoblastic leukemia or CNS leukemia had a higher risk of being admitted to the ICU in multivariable analyses, both for early admissions before the end of induction therapy and for all admissions during the study period.

CONCLUSIONS: The need for intensive care in children with acute lymphoblastic leukemia, especially for children with T cell acute lymphoblastic leukemia and CNS leukemia, is high with most admissions occurring during early treatment.

KEY WORDS: children; prevalence; intensive care; leukemia; risk factors

BACKGROUND

Leukemia is the most common childhood malignancy in Sweden (1). The most common childhood leukemia is acute lymphoblastic leukemia (ALL), with an prevalence of 4.2 per 100 000 children. The long-term survival rate in childhood leukemia has increased dramatically, from less than 10% in 1968 to current greater than 90% (1–3).

The high cure rate comes with a price, an increased risk for severe, potentially life-threatening adverse conditions that may require intensive care

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AT THE BEDSIDE

- Prognosis of pediatric ALL is favorable, but the need of supportive care is high. We explored the prevalence, risk factors, and outcome of intensive care in this patient group by combining two national quality registries.
- We show that 28% of children with ALL were admitted to the ICU at least once during first-line treatment, mostly during early treatment. Infections were an important reason for admission. Children with T-cell ALL or CNS leukemia had high risk of ICU admission.
- Although the need for interventions and supportive care in children with ALL is high, ICU mortality was low (6%). New immunologic treatment modalities may help to decrease the burden of severe infections in the future.

support, especially in the early treatment stages (4–6). Sepsis is the leading cause for ICU admission in pediatric cancer patients (7). However, several noninfectious complications may also require admission to the ICU (8–11). The outcome of children with hematologic malignancies admitted to the ICU has previously been poor (12, 13). With improved long-term prognosis of leukemia, better access to and advances in intensive care, the outcome for this patient group in the ICU has also improved (14).

The aim of this nationwide study was to explore the cumulative prevalence, underlying causes, risk factors, and outcomes of children with ALL admitted to the ICU under first-line leukemia treatment.

MATERIALS AND METHODS

The Swedish quality registries contain individualized data on patients, medical interventions, and outcomes, aimed at improving the quality of healthcare. This nationwide study used data from two different prospective Swedish national quality registries: the Swedish Childhood Cancer Registry (SCCR) and the Swedish Intensive Care Registry (SIR). Patients less than 18 years old diagnosed with ALL between July 2008 and December 2016 were initially identified from the SCCR. This cohort was then submitted to SIR for crosschecking.

For the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 leukemia treatment protocol, the SCCR also contains prospectively collected data on intensive care admissions during first-line treatment (10). Additional intensive care data were retrieved from the treatment centers by a questionnaire, a separate questionnaire was requested for each admission. SIR was linked with data from the SCCR and the questionnaires. In cases where there was a discrepancy with timing of admissions between the retrospective questionnaire data and the prospective SIR registry, the data from SIR with exact time of the day for admission and discharge were prioritized.

Data concerning sex, age, underlying malignancy, WBC count, CNS status at diagnosis, immunophenotype, stem cell transplantation (SCT), and status at last follow-up were retrieved from the SCCR. The CNS status was classified as follows: CNS1 (no identifiable leukemic blast cells in the cerebrospinal fluid by cytomorphology), CNS2 (> 0 and < 5 WBCs per μL identified as leukemic blast cells by cytomorphology), and CNS3 (≥ 5 WBCs per μL identified as leukemic blast cells by cytomorphology or signs or symptoms of CNS involvement). The questionnaire collected data on the main indication for admission to the ICU, time in the

RESEARCH IN CONTEXT

- We explored the prevalence, risk factors, and outcome after ICU admission in children with acute lymphoblastic leukemia (ALL) in Sweden by combining two national quality registries, Swedish Childhood Cancer Registry, and Swedish Intensive Care Registry.
- Twenty-eight percent of children with ALL were admitted to the ICU during first-line ALL treatment, especially during early treatment. Observation and infections were common reasons for admission. T-cell ALL and CNS leukemia were risk factors for ICU admission.
- Although ICU admission associated with decreased long-term overall survival, ICU mortality and the 30-day mortality after last discharge from the ICU was relatively low, 6% and 8%, respectively. We failed to identify risk factors for short-term mortality.

ICU, presence of neutropenia, positive blood cultures, and the need for mechanical ventilation or inotropes. Data from the SIR included the date of admission and discharge, main diagnosis, number of admissions, type of admission, and outcome (dead or alive) at discharge and 30 days after discharge. The data sources for variables used in this study are shown in **Supplemental Table 1** (http://links.lww.com/PCC/B802).

For the purposes of this study, admissions to the ICU were considered as a single admission if the patient had been transferred between different ICUs without discharge to a pediatric oncology ward in between the transfer. Only admissions while on first-line treatment (i.e., primary therapy before leukemia relapse, second malignant neoplasm, or before SCT, starting 5 d before to 3 yr after leukemia diagnosis) were included in this study.

The treatment protocol (NOPHO ALL2008) used for children 1–18 years old with B-cell precursor or T-cell ALL has been previously described (15, 16). Children younger than 1 year old at diagnosis were treated according to the Interfant-06 protocol, which is modified from the previously published Interfant-99 protocol (17), or the NOPHO ALL2014 Infant protocol, which is an age-adapted version of the NOPHO ALL2008 protocol. Philadelphia-positive ALL was treated as per the European intergroup study protocol on treatment of Ph+ALL (EsPhALL) protocol (18). Since the patients were treated based on different protocols, the National Cancer Institute criteria were used to classify patients under first-line treatment as nonhigh risk (initial WBC count < 50 × 10E9/L, age > 1 and < 10 yr) or high risk (initial WBC count > 50 × 10E9/L, age ≤ 1 or ≥10 yr). Remission was defined as less than 5% leukemic cells in the bone marrow at the end of induction, with adequate bone marrow cellularity and no evidence of disease at any other site.

The Regional Ethics Review Board in Stockholm approved the study's design to use the two Swedish national quality registries and collect additional data via a questionnaire, without the need for additional informed consent (approval no: 2017/1721-31/1).

Patient characteristics were summarized using descriptive statistics. Categorical data are presented as numbers and percentages (%), and continuous data as median (interquartile range [IQR] 25–75%). Categorical variables were compared using Fisher exact test.

For patient characteristics, disease- and treatment-related factors uni- and multivariable Cox regression analysis, estimating hazard ratios (HRs), was conducted to assess differences in cumulative prevalence of ICU admission. Time to the first ICU was defined as days from ALL diagnosis until the first ICU admission, with censoring for relapse, SCT, secondary malignancy, death, or end of follow-up, whichever came first. If the first ICU admission occurred within 5 days before diagnosis, time to the first ICU was defined as 0 days. The WBC count was transformed using natural logarithm in order to better fit the model assumptions and limit the influence of outliers. The method of Gray (1988) was used to estimate the cumulative prevalence of the first ICU admission in different risk groups, with death, SCT, relapse, and secondary malignancy as competing events, censoring at the end of follow-up (19). Overall survival (OS) was defined as days from diagnosis until death from any cause.

To evaluate the association between ICU admission and OS, an illness death model was used, with ALL diagnosis, ICU, and death as model states, using package mstate in R (20). Probabilities of being in each state at each specific time point were also estimated using the illness death model.

The association between 30-day mortality and clinical characteristics at ALL diagnosis was evaluated using logistic regression; the odds ratios for the 30-day mortality were estimated with cluster robust SEs and considering that some children had several ICU admissions. The 30-day mortality was defined as death in the ICU or death within 30 days of ICU discharge.

A two-sided *p* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 25 for Windows (IBM Corporation, Armonk, NY) and R statistical software (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Group and Data Collection

The whole cohort included 638 children with ALL; one was excluded due to SCT before leukemia diagnosis. In total, 28% (178/637 patients) had at least one ICU admission. The total number of the ICU admissions was 252 (median 1 admission per patient; IQR, 1–2; range, 1–6); one fourth of the patients (45/178 children) were admitted to the ICU more than once. The characteristics of the study participants are shown in **Table 1**.

TABLE 1.
Characteristics of the Study Group and Risk Factors for Admission to the ICU

	No ICU Admission (*n* = 459)	ICU Admitted (*n* = 178)	All Patients (*n* = 637)	Hazard Ratio (95% CI)	*p*
Median (IQR) age at diagnosis, yr [range]	4.2 (2.6–7.6) [0.4–17.9]	4.4 (2.8–8.6) [0–17.6]	4.2 (2.6–7.9) [0–17.9]	1.007 (0.974–1.041)[a]	0.68
Missing data	0	0	0		
Gender, *n* (%)					
Male	259 (56)	97 (54)	356 (55)	1 (reference)	0.76
Female	200 (44)	81 (46)	281 (45)	1.047 (0.779–1.407)	
Type of leukemia[b], *n* (%)					
B-cell precursor	406 (89)	133 (75)	539 (85)	1 (reference)	
T cell	38 (8)	39 (22)	77 (12)	2.805 (1.955–4.026)	**< 0.01**
Mixed phenotype acute leukemia	2 (0.4)	3 (2)	5 (0.8)		
Mature B	3 (0.7)	2 (1)	5 (0.8)		
Philadelphia + acute lymphoblastic leukemia	8 (2)	1 (0.6)	9 (1)		
Missing data	2	0	2		
National Cancer Institute risk group, *n* (%)					**0.03**
Standard risk	280 (62)	95 (54)	375 (59)	1 (reference)	
High risk	175 (38)	83 (47)	258 (41)	1.376 (1.024–1.850)	
Missing data	4	0	4		
CNS status at diagnosis, *n* (%)					
CNS1	387 (86)	127 (72)	514 (81)	1 (reference)	
CNS2	44 (10)	31 (17)	75 (12)	1.966 (1.327–2.913)	
CNS3	21 (5)	18 (10)	39 (6)	2.203 (1.344–3.610)	**< 0.01**
Missing data	7	2	9		**< 0.01**
Median WBC count at diagnosis (IQR) [range][c]	10.6 (4.8–44.4) [0.9–951.5]	18.8 (4.5–83.5) [0.7–1,161.0]	12.5 (4.8–53.7) [0.7–1,161.0]	1.167 (1.061–1.284)	**< 0.01**
Missing data	7	0	7		

IQR = interquartile range 25–75%.

[a]Hazard ratio (HR) for an 1 yr increase in age at diagnosis.

[b]Due to low number of cases with mixed phenotype acute leukemia and mature B leukemia, only patients with B-cell precursor and T cell acute lymphoblastic leukemia were compared.

[c]HR for a one-unit increase in the natural logarithm of WBC.

Demographic and clinical data on ALL were available for all patients from the SCCR. The SIR data were available for 96% ICU admissions (241/252) or 170 of 178 patients. Eight patients had data only from the SCCR ($n = 2$) or the SCCR and questionnaire ($n = 6$).

Of the 178 patients admitted to the ICU, ICU treatment was registered in the SCCR in 92 cases. The questionnaires were sent to the pediatric oncology centers concerning these 92 patients; data were available from 78 patients. In addition, the centers returned the questionnaires of nine patients with admissions not registered in the SCCR. Data from all three sources (data on leukemia treatment and clinical characteristics from the SCCR, data on intensive care from the SIR, and complementary data on the ICU by a questionnaire) were available in 46% children (81/178) admitted to the ICU (102/252 admissions); the SCCR and SIR data were available in 50% children (89/178) without the

questionnaire (139/252 admissions); questionnaire and SCCR data in 3% (six children) with nine admissions (one with missing social security number) and only SCCR data in two patients (1%) and two admissions. The data gathering process is shown in **Figure 1**.

Intensive Care Admissions

The main reason for ICU admission was observation, including pain relief, electrolyte disturbances, and postoperative care (41%; 89/219 admissions; missing data $n = 33$). In 19% of the admissions (41/219), the cause of admission was respiratory support, 28 of which were due to infection. Other causes were neurologic symptoms (11%; 24/219 admissions; one due to infection), and sepsis (10%; 21/219 admissions) (**Supplemental Table 2**, http://links.lww.com/PCC/B803).

The median time from leukemia diagnosis to the first ICU admission was 40 days (IQR, 0–144 d). When all admissions were considered, the median time to ICU admission was 67 days (IQR, 4–202 d). Almost half of the patients (48%; 85/178) needed intensive care before the end of the first month (induction therapy); 35% (63/178) were first admitted before or during the first week of diagnosis, and 30% (53/178) before or on the day of diagnosis.

The duration of stay in the ICU was less than 24 hours for the majority (53%; 94/174; missing data ($n = 4$) of the first admissions as well as for any admissions (56%; 138/248 admissions; missing data $n = 4$). The median duration of admissions for those who survived to

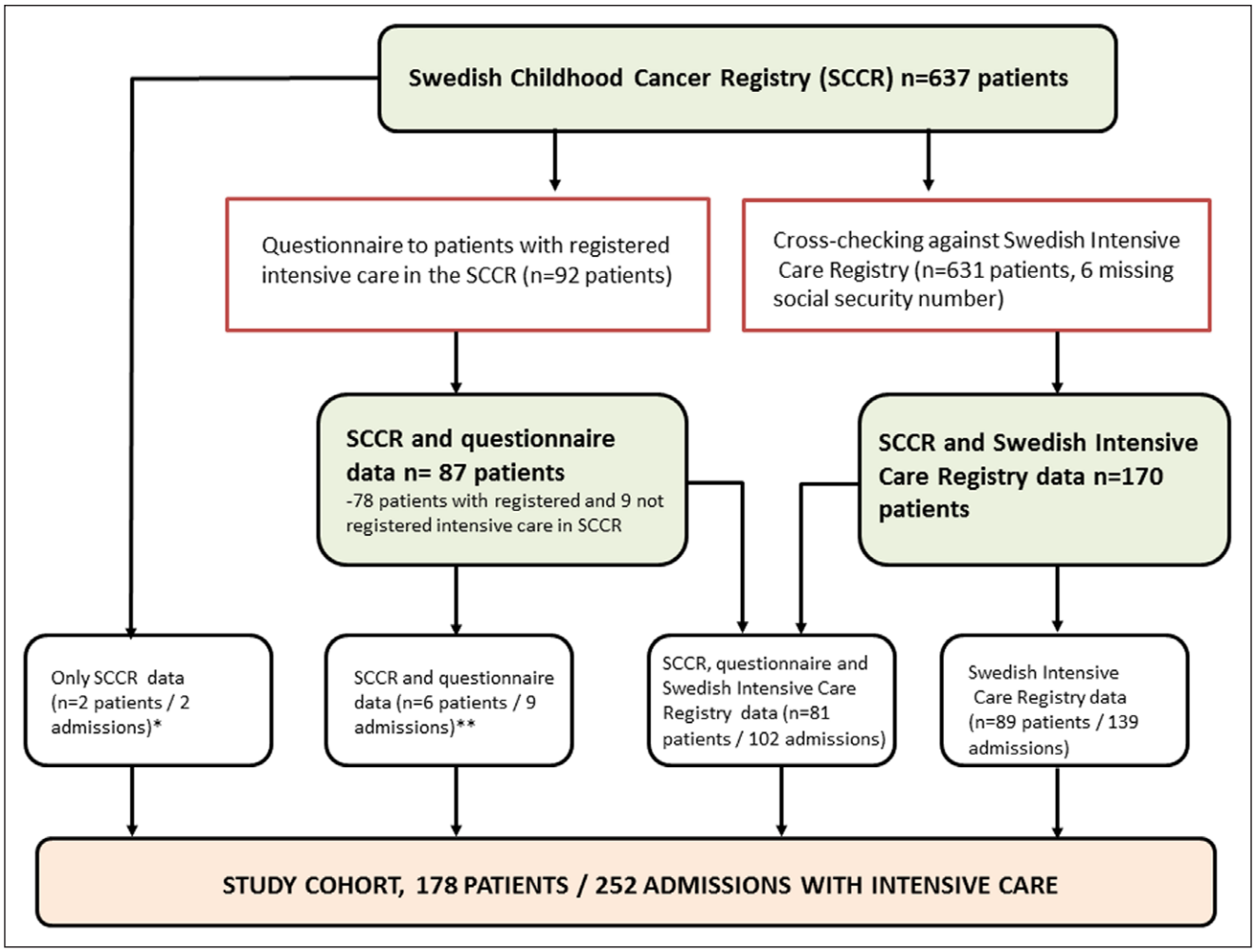

Figure 1. Flow chart demonstrating data gathering from the Swedish Childhood Cancer Registry (SCCR), patient charts, and the Swedish Intensive Care Registry. *One patient could not be linked to the Swedish Intensive Care Registry or medical records chart due to missing social security number and one patient received intensive care outside the university hospital; **data available from the questionnaire and the SCCR for six patients, one of whom could not be linked to Swedish Intensive Care Registry due to missing social security number.

discharge was 18 hours (IQR, 2–69 hr; range 0–4,080 hr; 232 admissions; missing data $n = 3$) as compared to 132 hours (IQR, 40–304 hr; range, 4–1,728 hr; 16 admissions) for those who died in the ICU ($p < 0.001$).

Most children, 57% (138/241 admissions; missing data = 11) were admitted from an inpatient ward, 27% (66/241 admissions) from the operation theater, 8% (20/241 admissions) via a pediatric emergency department, 4% (10/241 admissions) were transferred from another hospital, 1.6% (4/241 admissions) from another ICU, and another 1.2% (three patients) were admitted directly from home. Most patients were discharged to an inpatient ward (80%; 194/242 admissions; missing data = 10), 5% (12/242 admissions) were referred to another ICU, 6% (15/242 admissions) to another hospital, and on five occasions (2%), patients were discharged to home.

Risk Factors for Intensive Care

In the univariable analysis, patients with high-risk ALL, CNS leukemia at diagnosis, T-cell ALL, and high WBC count had a higher risk of being admitted to intensive care (Table 1). The results were similar when only patients admitted to the ICU before ALL diagnosis or under induction were compared with those not admitted to intensive care.

After adjustment for factors significant in the univariable analysis (risk group, immunophenotype, CNS involvement, and WBC count at diagnosis), only T-cell phenotype and CNS leukemia at diagnosis remained significant in a multivariable analysis, for all admissions in the whole cohort and those admitted before the end of induction therapy (**Table 2** and **Figure 2**).

Outcome After Intensive Care

The mortality in the ICU was 6% (16/251 admissions, time of the intensive care period not known for one nonsurvivor who died during early treatment due to bacterial infection), and the 30-day mortality after last discharge from the ICU was 8% (19/251 admissions). There was no difference in the 30-day ICU mortality between outpatients (admitted from the pediatric emergency department or home) and inpatients. ICU admission itself was associated with higher long-term mortality (HR for OS 3.25 [95% CI, 1.97–5.36]; $p \leq 0.0001$). Eleven of the 16 ICU deaths occurred during the first ICU admission. Most patients (75%; 12/16) died in the first complete remission, whereas four patients (25%) died before achieving first remission. Of the 459 patients who were not admitted to the ICU, six died during first-line treatment, either due to resistant disease ($n = 1$) or while in complete remission ($n = 5$). **Supplemental Figure 1** (http://links.lww.com/PCC/B804; **legend**, http://links.lww.com/PCC/B806) demonstrates the probability to be alive at various time-points of ALL treatment with and without intensive care.

None of the factors associated with risk of being admitted to the ICU (high-risk ALL, high WBC count, CNS involvement at diagnosis, and T-cell ALL) were associated with higher mortality within 30 days of discharge from the ICU (**Table 3**). Patients with two or more admissions did not have significantly worse 30-day survival than those admitted once.

Comparison of Data From Different Sources

Of all the 170 patients with data available on patient characteristics and ALL from SCCR and on intensive care from SIR, 48% (81/170) had supplementary data from a questionnaire (Fig. 1). When only children with data available from all the three sources were included, 13% (81/637 patients) had at least one ICU admission.

TABLE 2.
Multivariable Hazard Ratios of Clinical Risk Factors for Admission to the ICU

Clinical Characteristics	Hazard Ratio (95% CI)	*p*
Type of leukemia		
B-cell precursor	1 (reference)	
T cell	2.328 (1.524–3.554)	**< 0.01**
National Cancer Institute risk group		
Standard risk	1 (reference)	
High risk	1.036 (0.698–1.539)	0.86
CNS status at diagnosis		
CNS1	1 (reference)	
CNS2	1.723 (1.136–2.615)	**0.01**
CNS3	1.877 (1.112–3.168)	**0.02**
WBC at diagnosis[a]	1.015 (0.895–1.151)	0.82

[a]Hazard ratio (HR) for a one-unit increase in the natural logarithm of WBC.

HRs adjusted for type of leukemia, National Cancer Institute risk group for primary treatment, CNS involvement, and WBC count at diagnosis.

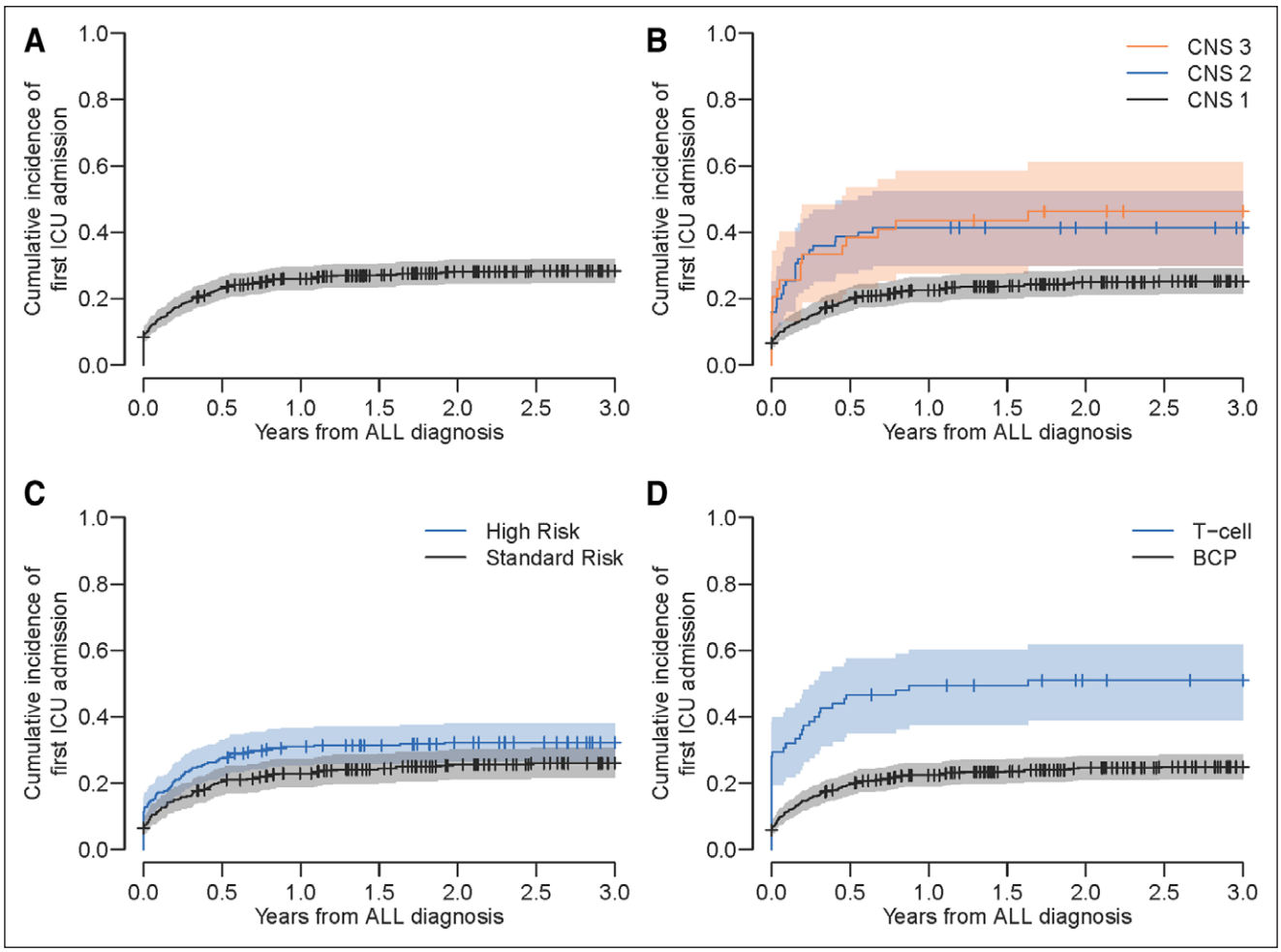

Figure 2. Cumulative prevalence of the first intensive care admission (**A**) all patients, (**B**) by CNS status at acute lymphoblastic leukemia (ALL) diagnosis, (**C**) by ALL risk group, and (**D**) by immunophenotype. BCP = B-cell precursor.

There was no difference in age, WBC count at diagnosis, immunophenotype, CNS involvement, or sex between patients admitted to the ICU with (n = 81) and without (n = 89) the questionnaire data. However, the prevalence of high-risk leukemia was higher in patients with data from all sources (57%; 46/81) than in those with data from only SCCR and SIR (36%; 32/89, p = 0.009), and the ICU stay was longer (median 53 and 4 hr, respectively; $p < 0.001$). Data from questionnaires are shown in **Supplemental Table 3** (http://links.lww.com/PCC/B805).

In admissions with data from the SCCR and SIR, but lacking the questionnaires, observation was more often the main reason for admission when compared with those with data from all sources (61/108 admissions; missing data = 31 and 21/102, respectively; $p < 0.001$). When patients with data from all three data sources were compared with those with no ICU admissions, high-risk ALL, CNS involvement at diagnosis, T-cell ALL, or high WBC count were associated with higher risk for intensive care. In multivariable analysis, only T-cell ALL (p = 0.017; HR, 2.133 [95% CI, 1.147–3.967]) and CNS 3 status ($p < 0.001$; HR, 3.058 [1.583–6.013]) reached statistical significance.

DISCUSSION

Despite improved prognosis for childhood ALL, leukemia- and treatment-related complications remain a major challenge. In our cohort, 28% of all children required intensive care, 8% before or on the day of ALL diagnosis. ICU mortality was 6%, and most of these patients were in remission. T-cell ALL and CNS involvement at diagnosis were associated with admission to the ICU, but we failed to show association with higher ICU mortality.

An American study in children with both hematologic malignancies and solid tumors reported a high admission rate (38%) to intensive care (21). Our ICU admission rate of 28% was comparable with the

TABLE 3.
Clinical Characteristics of the Survivors and Nonsurvivors Within 30 Days of Discharge From the ICU Under Primary Treatment for Acute Lymphoblastic Leukemia

Clinical Characteristics	Survivors		Nonsurvivors		OR (95% CI)	p^b
	n = 158 Patients	*n* = 231 Admissions	*n* = 18 Patients	*n* = 19 Admissions		
Median age at leukemia diagnosis, yr (IQR); range	4.1 (2.6–8.1); 0–17.6	3.9 (2.3–8.0); 0.0–17.6	5.9 (3.2–12.6); 1.0–16.2	5.6 (3.2–11.8); 1.0–16.2	1.10 (0.98–1.23)	0.092
Gender, *n* (%)						
Male	88 (56)	116 (50)	7 (39)	7 (37)	1 (reference)	0.75
Female	70 (44)	115 (50)	11 (61)	12 (63)	0.82 (0.25–2.72)	
Type of leukemia[a], *n* (%)						
B-cell precursor	119 (75)	181 (78)	14 (78)	15 (79)	1 (reference)	0.82
T cell	34 (22)	42 (18)	4 (22)	4 (21)	1.15 (0.36–3.70)	
Mixed phenotype acute leukemia	3 (2)	4 (2)	–	–		
Mature B	2 (1)	4 (2)	–	–		
National Cancer Institute risk group, *n* (%)						
Standard risk	89 (56)	120 (52)	6 (33)	6 (32)	1 (reference)	0.11
High risk	69 (44)	111 (48)	12 (66)	13 (68)	2.34 (0.83–6.58)	
CNS status at diagnosis, *n* (%)						
CNS1	113 (71)	156 (68)	13 (76)	13 (72)	1(reference)	
CNS2	29 (18)	53 (23)	2 (12)	2 (11)	0.45 (0.09–2.19)	0.32
CNS3	16 (10)	22 (10)	2 (12)	3 (17)	1.64 (0.33–8.21)	0.55
Missing data	–	–	1	1		
Median WBC count at diagnosis (IQR); range	16.6 (4.4–76.4); 0.7–1,161	16.3 (4.5–82.6); 0.7–1,161	66.0 (12.6–170.5); 2.0–584.0	61.2 (15.2–139.0); 2.0–584.0	1.21 (0.93–1.58)	0.15

IQR = interquartile range 25–75%, OR = odds ratio.

[a] Due to low number of cases with Mixed phenotype acute leukemia and mature B leukemia, only patients with B-cell precursor and T cell acute lymphoblastic leukemia (ALL) were compared.

[b]The analyses are based on intensive care admissions.

Two patients were excluded from analyses due to missing data on intensive care, one of whom died under ALL treatment.

American study but considerably higher than an Italian single-center study reporting an admission rate of only 7% in 507 children with only hematologic malignancies (22). Different criteria for ICU admission and registration can partly explain the discrepancies in ICU admission rates. Our study cohort included children admitted and registered either in the SIR and/or SCCR. Coverage of the SIR data was high; 96% of ICU admissions had the SIR data, whereas the supplementary questionnaire data were lacking in more than half all admissions. The group with data from all sources had significantly more high-risk patients and longer treatment times, suggesting registration bias. A likely explanation is that short-term admission for observation (e.g., after interventions) was not considered as intensive care by the treating pediatric oncologist and

therefore was not registered in SCCR. However, even if only patients for whom data were available from all three sources were considered, the admission rate would still be 13%, highlighting the high demand for supportive care resources in this patient group.

In our study, patients with T-cell ALL and CNS leukemia had higher risk for admission to the ICU, but we could not show association with higher ICU mortality. CNS leukemia and T-cell immunophenotype have been associated with acute CNS toxicity, increased need for intensive care, and thrombosis (23–26). A previous Nordic study showed that patients with T-cell ALL had higher risk for treatment-related mortality, but this could not be demonstrated in another large study from the United States (5, 27). CNS leukemia and T-cell immunophenotype often exhibit more aggressive disease and receive more intensive chemotherapy and are therefore at a higher risk for infection, the second most common reason for ICU admission in our cohort.

A recent meta-analysis of 31 observational studies over the past 30 years showed high mortality in the PICU for children with cancer (28%). When excluding postoperative patients, the mortality rate increased to 33% and was even higher in patients with sepsis (46%). They only observed a slight decrease in mortality over the decades when postoperative patients were not included (28). The 6% mortality at discharge observed in our cohort was substantially lower, but our cohort also included postoperative patients. Another large multicenter study reported mortality more in line with our study, with children with hematologic cancer having higher mortality than those with solid tumors (10% and 5%, respectively) (14). However, as general survival from leukemia per se has increased, the fraction of children dying from therapy-related toxicity has also increased.

Almost one fourth of all admissions were related to infection. Infections may have contributed also to other reasons for admission. Severe complications requiring intensive care also cause delays in leukemia treatment and may jeopardize long-term survival. New immunologic treatment modalities, such as blinatumomab (3, 29), may help to decrease the severe infections and, consequently, treatment-related mortality.

The main limitation of our study is a lack of chart review and missing SCCR ICU admission data for half of the patients. Although multiple data sources allow better coverage of the ICU occasions, it can also create registration bias due to different criteria for registration, as indicated by the lower number of high-risk patients with shorter treatment times in patients with missing questionnaire. Additionally, as the number of deaths within 30 days of discharge was low, the results on mortality analyses should be interpreted with caution.

The strength of this study stems from the focus on the patient group with one cancer type and the combination of two Swedish quality registries. With this approach, we believe that we covered practically all ICU admissions of children with ALL. Furthermore, our dataset included detailed clinical data on leukemia, chemotherapy, and response to leukemia treatment, including long-term outcome combined with details on intensive care treatment.

In conclusion, a considerable number of children with ALL require intensive care, especially at diagnosis and during early treatment. There was a discrepancy between registered ICU admission between SIR and SCCR, with short admissions typically missing from SCCR where focus has been on ALL-related data. T-cell phenotype and CNS involvement were associated with higher risk for admission to intensive care, but not with poor short-term outcome. Infections were a common reason for admission. Our results highlight the need for new, less toxic treatment modalities that may help to reduce the burden of severe infections.

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1 *Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden.*

2 *Pediatric Oncology, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden.*

3 *ECMO Centre Karolinska, Department of Pediatric Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm, Sweden.*

4 *Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden.*

5 *Institution of Clinical Sciences, Department of Pediatrics, Sahlgrenska University Hospital, Gothenburg, Sweden.*

6 *Department of Anesthesia, Södertälje Hospital, Södertälje, Sweden.*

7 *Department of Anaesthesia and Intensive Care, Karolinska Institutet at Danderyd Hospital (KIDS), Danderyd, Sweden.*

8 *Department of Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden.*

9 *Department of Women's and Children's Health, Uppsala University and Pediatric Oncology, Uppsala University Hospital, Uppsala, Sweden.*

10 *Department of Pediatric Oncology, Skåne University Hospital, Lund University, Lund, Sweden.*

11 *Department of Pediatrics, Linköping University Hospital, Linköping, Sweden.*

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For information regarding this article, E-mail: susanna.ranta@ki.se

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