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RESEARCH ARTICLE

### Anthracycline-related cardiotoxicity in patients with acute leukemia and down syndrome: A retrospective study

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### ABSTRACT

Background: Down Syndrome (DS) is a predisposing syndrome for leukemia. Patients with Down syndrome (DS) have acute leukemia characterized by unique toxicity profiles and treatment responses. Achieving a balance between potential toxicities and curative treatments is challenging. The purpose of this research was to identify potential risk factors and the incidence of clinical cardiotoxicity following Anthracycline therapy in DS with acute leukemia. Patients and Methods: From January 2011 to December 2019, 32 pediatric patients with DS and acute leukemia were recruited for this retrospective study at Cairo University's National Cancer Institute (NCI). The study excluded patients above 18 years old, those who had already received treatment, and those with missing data. Cardiotoxicity was reported according to the Common Terminology Criteria of Adverse Events (CTCAE), version 5.0. Results: Of the 32 individuals diagnosed with DS and acute leukemia, eight patients (25%) had acute myeloid leukemia (AML), 24 (75%) had acute lymphoblastic leukemia (ALL), and 18 (56%) had associated congenital cardiac defects (CHD). The median age was 3.25 years. All patients with AML had CHD, whereas 41.7% (10/24) of ALL patients had CHD. Clinical cardiotoxicity was reported in 16 patients (50%) and was more common in individuals with CHD compared to patients with structurally normal hearts, as 75% (12/16) of patients who had cardiotoxicity had concomitant CHD. Conclusion: Leukemic patients with Down syndrome and congenital heart disease are more susceptible to Anthracyclineassociated cardiotoxicity than patients with DS and structurally normal hearts.

Keywords: Cardiotoxicity, congenital heart disease, Down syndrome, Leukemia

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### INTRODUCTION

Down syndrome (DS) is characterized by a distinct range of malignancies wherein the incidence of leukemia is greater than that of solid tumours. The incidence of acute leukemia associated with DS has been reported to range between 1:100 and 1:220 (Xavier et al., 2009). Human chromosome 21 (HSA21) is the smallest human autosome harboring Down syndrome critical regions (DSCRs 21q22.3) containing approximately 30 genes thought to be responsible for major DS features and increased risk of leukemia. The DSCR1 protein, also named Regulator of Calcineurin A (RCAN1) is highly expressed in brain and heart which can explain mental retardation and cardiac defects (Fuentes et al., 1995). DS myocardium has greater expression levels of the chromosome 21 gene carbonyl reductase1 (CBR1), located in the DSCR (21g22.12). (CBR1) increases the production of cardiotoxic Anthracycline alcohol metabolites which are forty times more cardiotoxic than their parent Anthracyclines (Kalabus et al., 2010). Also, Superoxide dismutase 1, located in chromosome 21, promotes the production of hydroxyl free radicals, making DS cells more susceptible to apoptosis (Rabin and Whitlock, 2009). Pediatric DS patients, particularly those with acute myeloid leukemia-DS (AML-DS), are at a 3.4-fold increased relative risk for acute and chronic Anthracycline-related cardiotoxicity. Because Anthracyclines are fundamental to the majority of leukemia treatment protocols, cardiotoxicity

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### Copyright

©2024 Nashwa Ezz Eldeen, Mariam Mikhael, Hend A. Nooh, Mona S. El Ashry, Asmaa Hamoda. This is an Open Access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any format provided that the original work is properly cited. must be considered seriously. Anthracycline cumulative total dose, young age, and female gender are all risk factors for Anthracyclinerelated cardiotoxicity (Ravindranath, 2005). The approach of decreasing the cumulative dose of Anthracycline by 25% was implemented in the Children's Oncology Group (COG): AAML0431 trial. This dose reduction effectively minimized the risk of adverse cardiac events while leaving patients' outcomes unaffected (Taub et al., 2017). Trisomy 21 has been proposed as a potential risk factor for cardiotoxicity induced by Anthracycline. Still, data is limited and contradictory (Hefti and Blanco, 2016). This research aimed to explore possible risk factors and determine the occurrence of clinical cardiotoxicity after Anthracycline treatment for patients with acute leukemia and Down syndrome.

### METHODOLOGY

### Patients and study design

A retrospective cohort study was performed at the National Cancer Institute (NCI), Cairo University, Egypt, that includes all pediatric down syndrome (DS) patients diagnosed with acute leukemia from January 2011 to December 2019 (nine years), patients were followed up till June 2022. Patients who have been diagnosed and treated at NCI. with the disease confirmation by morphology and immunophenotyping in the bone marrow, and less than 18 years old meet the inclusion criteria. All previously treated patients and patients' records with incomplete data were excluded. Informed consent was obtained from the legal guardians patient's upon hospital admission for the possible use of their data in future research, and the local ethical committee approved the study.

### **Treatment protocols**

**Treatment of DS-ALL protocol (illustrated roadmap in appendix A):** Acute lymphoblastic leukemia (ALL) –DS patients were treated according to modified St. Jude total XV protocol. All patients received induction phase in which Doxorubicin was given (25mg/m<sup>2</sup>/dose) at Day 1 & 8. *Consolidation Therapy:* four courses of high dosage Methotrexate (HDMTX) with modification of HDMTX (500 mg/m<sup>2</sup>). *Maintenance treatment in ALL-DS patients:*  Maintenance therapy is composed mainly of methotrexate (MTX) and 6-mercaptopurine (6MP). According to risk stratifications, ALL –DS low risk patients received another dose of Doxorubicin (30mg/m<sup>2</sup>) at week 7 reinduction with total cumulative dose 80 mg/m<sup>2</sup> while standard risk cases received more frequent dose in week 1,4,7,8, 11 & 14 (30mg/m<sup>2</sup>) with total cumulative dose 230 mg/m<sup>2</sup>.

Treatment of DS-AML protocols (illustrated roadmap in appendix B): DS Patients with AML less than four years are treated according to the COG Protocol AAML0431(Taub et al., 2017) with the following modifications according to availability: Daunorubicin was replaced with Doxorubicin (With the same dose) and 6thioguanine was replaced with 6-MP (with the same Dose). The treatment consisted of 4 cycles of induction therapy and two cycles of intensification therapy. In induction cycles I, III, and IV patients received Doxorubicin intravenous (IV) infusion for 96 hours 0.67 mg/kg/24 hours for patients < 36 months of age or 20 mg/m<sup>2</sup>/24 hours for patients > 36 months of age, Induction cycle II, Intensification cycles I and II didn't contain any Anthracycline. For patients over the age of 36 months, the total cumulative dose of Doxorubicin is 240 mg/m<sup>2</sup>. DS-AML patients older than four years were treated according to the Non-DS AML protocol (adopted from COGAAML-0531) with a total cumulative dose of Anthracycline 252 mg/m<sup>2</sup>. (illustrated roadmap in Appendix C).

### **Cardiotoxicity definitions**

**Chemotherapy-induced Cardiotoxicity** was defined according to European Society of Medical Oncology (ESMO): A decline of ejection fraction (EF) 5% to final EF 55% with symptoms of congestive heart failure (HF) or an asymptomatic decline of left ventricular ejection fraction (LVEF) 10% to below 55% EF (Curigliano et al., 2012).

**Early cardiotoxicity:** Cardiotoxicity that occurred within one year of Anthracycline treatment (Cardinale et al., 2015).

**Time points of evaluation of cardiotoxicity** by echocardiography (ECHO) were done periodically during and after leukemia therapy. A baseline evaluation was performed before

initiation of Anthracycline therapy. Subsequent evaluations were performed before each time of administration of Anthracyclines and at the end of treatment. Results of the initial baseline and subsequent echocardiography and clinical data were documented.

Cardiotoxicity was classified according to Common Terminology Criteria of Adverse Events CTCAE v5.0 (NCI, 2017), where grade III was defined as symptomatic due to a drop in EF responsive to intervention (e.g., diuretics, inotropic therapy that Increases cardiac contractility, for example, Dobutamine and milrinone, afterload reducing agents like captopril), Grade IV was defined refractory or poorly controlled HF due to drop in EF; intervention such as ventricular assist device, intravenous vasopressor support include phenylephrine, epinephrine, norepinephrine and vasopressin and grade V was defined as due to left ventricular death systolic dysfunction. The ejection fraction was calculated using the M-mode method.

### **Outcome measures**

Anthracycline-induced cardiomyopathy was classified as patients who have one of the following outcomes: Death, Alive with anticongestive treatment and Recovery without the current requirement for anti-failure therapy but previous anti-failure treatment. The Overall Survival was measured from the date of diagnosis to the date of last follow-up or to the date of death from any cause.

### **Statistical analysis**

The statistical analyses were performed using the IBM Statistical Package for Social Sciences (SPSS) version 28 software for the Windows operating system. Categorical variables are represented by frequencies and percentages, whereas numerical variables are represented by median and range in descriptive statistics. The Chi-square test was employed to compare categorical data, whereas the Mann-Whitney U test was utilized for numeric variables.

The Kaplan-Meier method was employed to do survival analysis. A P-value less than 0.05 is deemed to be statistically significant.

### RESULTS Patients Characteristics

A total number of 32 patients with Down syndrome and leukemia were enrolled in the study after the exclusion of 2 patients. The age ranged from 1 to 17 years with a median 3.25 years. There were 8 AML patients (25%), and 24 (75%) had ALL. Twenty-three (72%) patients were boys (17 ALL & 6 AML), and nine (28%) were girls (7 ALL & 2 AML). Eighteen patients (56%) had associated CHD; one of them had corrective open-heart surgery before the diagnosis of leukemia. Patients with AML had a higher incidence of CHD compared to ALL (100% versus 41.7%, P-value = 0.004). Clinical cardiotoxicity developed in 16 patients (50%). Most of the patients (75%) who developed cardiotoxicity had CHD, though only three patients required cardiac medications at baseline before starting treatment. Six patients were classified as grade III left ventricular systolic dysfunction, while three patients were grade IV, and seven patients were grade V (Table 2).

One ALL-DS patient did echocardiography at the end of treatment and showed normal cardiac function, but he developed pulmonary hypertension grade II according to CTCAE v5.0. that pulmonary Cardiologist suggested hypertension may be due to upper airway obstruction and obesity that lead to chronic hypoxia and may cause pulmonary hypertension even without having CHD, started 0.3mg/kg/day, sildenafil Captopril, and Spironolactone. 2 years later sildenafil was stopped, and the patient continued Captopril and Spironolactone.

The outcome of Anthracycline-induced cardiomyopathy was classified as 7 cases ended with death by refractory heart failure, 5 cases were alive with anti-failure treatment, and 4 cases received anti-failure treatment but recovered without a current requirement for anti-failure therapy as illustrated in Table 2. Eleven cases out of 24 patients of ALL-DS experienced cardiotoxicity, representing 45.8% of the DS-ALL patients, while 65.25 % (5/8) of DS-AML experienced cardiotoxicity. There were no statistically significant differences regarding cardiotoxicity between AML and ALL patients,

which may be due to the small sample size (Table 1). Patients with associated CHD were more vulnerable to cardiotoxicity compared to others (Table 1, Figure 1). Although the late survival seems to be higher in patients without cardiotoxicity as the cumulative survival at 2 years was 41.7 % for DS-AL without cardiotoxicity versus 25% for those having cardiotoxicity, but the overall survival between patients who had cardiotoxicity and those without cardiotoxicity was comparable (logrank P 0.304), as shown in Figure 2.

### DISCUSSION

Children with DS are more likely to develop acute leukemia. Treatment of DS who have leukemia is challenging since they are more vulnerable to severe complications. Few studies analyzed the outcome & cardiotoxicity with DS and acute leukemia. This retrospective study covered nine years at NCI of Egypt and included a total of 32 patients with acute leukemia and DS. Anthracyclines remain effective drugs in leukemia treatment, yet their cardiotoxic effect is still challenging.



Figure 1. The incidence cardiotoxicity in both DS patients with and without congenital heart disease.



Figure 2. Correlation of OS & incidence of cardiotoxicity in studied group.

Anthracycline dose can be measured using the most recently published doxorubicin equivalents ratios for late-onset cardiotoxicity inform of daunorubicin 0.5; epirubicin 0.8, idarubicin 5, and mitoxantrone10 (Feijen et al., 2019). Different definitions were reported for cardiotoxicities as Cardiovascular toxicities of cancer therapies include a large scale of entities. The International Cardio-Oncology Society defines cardiovascular toxicities as the most common adverse Cardiovascular events during cancer therapy into five main classes: (i) cardiac dysfunction: cardiomyopathy/heart failure (HF), (ii) myocarditis, (iii) vascular toxicity, (iv) hypertension, and (v) arrhythmias and QTc prolongation (Herrmann et al., 2022).

Male to female ratio in this study was 2.4:1, with a predominance of male DS-ALL patients similar to Bourusly et al. (2017), Buitenkamp et al. (2014) also showed a predominance of males (male to female ratio 1.1: 1), while Schmidt et al. (2021) study which contained 21 DSleukemia patients, there was female predominance in DS -ALL and male: female ratio (1:1.8). Out of 32 included patients, there were 8 (25 %) patients were DS-AML, and 24 (75%) patients were DS-ALL; there was a higher incidence of CHD in DS-ALL patients (41.7%) when compared to Ayad et al. (2017) and Schmidt et al. (2021) (33.3% and 35% respectively). Also, all cases of AML-DS (100%) in our study had CHD, while O'Brien et al. (2008) studied a cohort of DS-AML with a higher number of DS-AML (n=57 patients) & reported that 42% with DS-AML had documented CHD. Although we have a higher incidence of CHD in both ALL & AML, as mentioned before, which represent 56% of the whole studied group, we demonstrated a higher incidence of CHD in the AML-DS group with statistically significant Pvalue.

In O'Brien et al. study (2008), they prospectively assessed their DS-AML patients after receiving a standard-therapy arm of POG 9421 with a total dose of Daunorubicin 135 mg/m2 and Mitoxantrone 80 mg/m2. Cardiomyopathy was defined as clinically symptomatic congestive heart failure (CHF) that mandated any medical intervention (e.g., diuretics, inotropic therapy, and afterload reduction) or dilated cardiomyopathy at autopsy.

Parameter	No Cardiotoxicity (N=16)	Cardiotoxicity (N= 16)	P value					
Age, months	42 (12-187)	47 (12-205)	1.00					
Gender, n (%)								
Male	10 (43.)	13 (56.5)	0.433					
Female	6 (66.7)	3 (33.3)						
Diagnosis, n (%)								
ALL	13 (54.2)	11 (45.8)	0.685					
AML	3 (37.5)	5 (62.5)						
Congenital heart disease, n (%)	6 (33.3%)	12 (66.7)	0.003					
Cumulative dose of Anthracycline mg/m2	80 (25-280)	80 (25-230)	0.468					
EF before chemotherapy, (%)	70(68.5-71.5)	71.5(69.5-73)	0.184					
EF after chemotherapy, (%)	70(68-70)	70(68-70)	<0.001					
Survival, n (%) at 2 years	41.7	25	0.304					
Abbreviation: ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, EF: ejection fraction.								

Table 1. The clinical characteristics of the studied groups.

In their study, clinically symptomatic cardiomyopathy was reported in ten patients (17.5%) with DS-AML. Fifty percent of them had CHD & mortality reported in three cases from cardiomyopathy; one patient had a functionally insignificant ASD and other required cardiac medications at initial treatment. In our DS-AML cohort, we reported a much higher incidence as 62.5% of DS-AML had clinical cardiomyopathy & documented cardiotoxicity.

In comparison, 75% of children with CHD had cardiotoxicity; three patients required cardiac medications at baseline despite a much lower dose of Anthracycline. Indeed, all DS pediatric patients received Anthracycline in the form of at least 50mg/m2 Doxorubicin during induction in ALL-DS patients. In contrast, cases of AML-DS patients received a total dose of Doxorubicin 240 mg/m<sup>2</sup> in the whole protocol for patients younger than four years old and 252 mg/m<sup>2</sup> if older than four years. In POG 9421, the authors used a total cumulative dose of Anthracyclines of 535 mg/m<sup>2</sup> after using an empirical 5:1 conversion factor for Mitoxantrone (O'Brien et al., 2008) which is much higher than the dose given in our DS-AML protocol (315 mg/m<sup>2</sup>) if we use the same conversion factor.

COG conducted AAML0431 trial in 204 DS-AML under the age of 4 years with a much lower incidence of cardiotoxicity, also with no lifethreatening cardiac toxicity; they had only seven cardiac adverse events inform of  $\geq$  grade 3 (sinus tachycardia, 3; pericardial effusion, 1, prolonged QT- 1) or grade 4 (pericardial effusion 1; cardiac arrest, 1) (Taub et al., 2017). This trail was given for DS-AML patients underage of 4 years in our study with same doses with few modifications with occurrence of cardiotoxicity in 5/8 patients (62.5%) so we are suggesting occurrence of contributing factors in our cohort other than toxic effect of Anthracycline.

Sorrell et al. (2012) completed phase 3 of a clinical trial COG A2971, which enrolled 132 DS patients with either AML (n = 91) or myelodysplastic syndrome (n = 41). In their study, Children with ML-DS received a cumulative Anthracycline dose of 320 mg/m2. Cardiotoxicity was identified in Seven individuals (5.3%) who developed grade  $\geq$  3 cardiotoxicity (Sorrell et al., 2012). In our study received slightly higher total DS-AML cumulative dose of Anthracycline (240 mg/m<sup>2</sup> in patients less than 4 years & 252 mg/m<sup>2</sup> for cases older than 4 years) but with higher incidence of grad III cardiotoxicity (2/8) which accounts for 25% of DS-AML cohort.

In our study, out of sixteen patients who developed cardiotoxicity, six patients were classified as grade III left ventricular systolic dysfunction, three patients were grade IV, and seven patients were grade V. Uffman et al. (2017) published the results of the international ML-DS2006 trial in 2017; they had two mortality cases by cardiac failure, so they emphasized the hypersensitivity of DS patients to cardiotoxic drugs and recommended using liposomal formulations; patients in this study had received 315mg/m<sup>2</sup> of Anthracycline (34 mg/m<sup>2</sup>) Idarubcine - 14 mg/m<sup>2</sup> Mitoxantrone). Taga et al. (2011) reported marvelous results in the JCCSLG AML 9805 Down study without the occurrence of any cardiotoxicity grad III/IV<sup>[20]</sup>;

case	Sex	Leukemia type	Age (months)	Type of CHD	Baseline cardiac medications	Onset of Symptoms	Symptoms	Treatment	Outcome
1	м	ALL	50	None	None	End of Therapy	Dyspnea on excretion	Sildenafil – captopril- Spironolactone	Alive with anti-failure treatment.
2	м	ALL	173	ASD, VSD normal function	None	Post-week 72 maintenance therapy of TXV	Shock, EF: 50 / FS:20	vasopressor (adrenaline)	Recovery without anti- failure treatment
3	м	ALL	51	None	None	24 days of induction therapy	Respiratory failure and shock	Intubation, pressors,	Death
4	м	ALL	30	None	None	18 days of induction therapy	Shock left dilated ventricle	Intubation, pressors,	Death
5	M	ALL	30	None	None	14 days of induction therapy	Pulmonary edema ; EF:42% / FS 15%	Intubation, pressors,	Death
6	М	ALL	73	History of VSD corrected by open Heart surgery	Furosemide, captopril	13 days of induction therapy	Respiratory failure; shock	Intubation, pressors (adrenaline)	Death
7	F	ALL	50	ASD, normal function	None	31 days of induction therapy	Weak pulsation, hypotension, poor perfusion	Intubation, pressors (adrenaline)	Death
8	F	ALL	49	VSD,	None	Post-week 1 maintenance therapy of TXV	Not reported (accidentally discovered by Echo before administration of doxorubicin)	Captopril	Recovery without anti- failure treatment and still alive
9	м	ALL	205	None	None	Post-week 17 maintenance therapy of TXV	tachycardia	Captopril	Recvery without anti- failure treatment and still alive
10	м	ALL	39	ASD 3mm, normal function	Furosemide, captopril	22 days of induction therapy	Generalized edema, hypotension	pressor (adrenaline)	Death
11	М	ALL	46	None	None	Post week 9 maintenance therapy of TXV	Cardiogenic shock	pressor (adrenaline)	Alive with anti-failure treatment, but died later on due to sepsis
12	F	AML	12	ASD, normal function	None	Post induction II	Not reported (accidentally discovered by Echo before administration of doxorubicin	(captopril- Spironolactone)	Alive with anti-failure treatment, but died later on due to sepsis
13	м	AML	28	ASD, normal function	None	Post induction II	Shock, EF: 48 / FS:23	(adrenaline)	Alive with anti-failure treatment, but died later due to sepsis which worsened the cardiac condition
14	Μ	AML	156	ASD, normal function	None	Post induction I	Not reported (accidentally discovered by Echo before administration Of next dose of doxorubicin)	Captopril	Alive with anti-failure treatment, but died later due to sepsis which made the cardiac condition worse
15	M	AML	15	VSD, impaired function	captopril	D4 induction I	Respiratory failure; shock	Intubation, pressors (adrenaline)	Death
16	Μ	AML	30	The previous history of ASD, PFO closed spontaneously	None	Post-cycle I induction And function improved then decline again post cycle III	Post cycle I >> accidentally discovered, while Post-cycle III cardiogenic shock	Post cycle I >> captopril Post-cycle III requires inotropic support (Dobutamine)	recovery without the current requirement for anti-failure therapy and still alive

### Table 2. Characteristics of the 16 patients with symptomatic cardiotoxicity

this study was piloted to assess the efficacy and safety of continuous 100 mg/m<sup>2</sup>/day for seven davs Cytarabine together with Pirarubcin/Mitoxantrone for AML-DS patients. They had 24 AML patients younger than four years. Despite the small number of patients, the regimen was highly promising because there were no non-responders and only one case of relapse; they used a minimum dose of cardiotoxic drugs with a cumulative dose of Anthracycline 138mg/m<sup>2</sup> after using the most recently published doxorubicin equivalents ratios for late-onset cardiotoxicity (Feijen et al., 2019).

We investigated various factors that led to a higher incidence of cardiotoxicity in our cohort than in previous studies; we found that the occurrence of CHD is an important predisposing factor for cardiotoxicity, which was more prevalent in our cohort than in others. We also found a higher incidence of cardiotoxicity in males than females (56.5% vs33.3%). In addition, cases of DS-AML have a higher incidence than DS-ALL (62.5% vs 45.8%); however, the P-value was not significant, which may be related to the small sample size in two previous comparisons. We investigated the effect of cardiotoxicity on survival. Although the late survival seems to be higher in patients without cardiotoxicity, the overall survival between patients who had cardiotoxicity and those without cardiotoxicity was comparable (log-rank P 0.304), as shown in Figure 2.

As mentioned, before we recommend utilization of more advanced echocardiographic techniques such as tissue Doppler imaging and speckle tracking echocardiography for follow up cases of DS during course of acute leukemic treatment which could detect even subtle changes in cardiac function, we also recommend more frequent monitoring if the patient proved to have CHD.

**Limitations** The study was limited by a small sample size, and the assessment of cardiotoxicity only relied on the reduction in EF.

### CONCLUSION

Pediatric patients with Down syndrome and congenital heart disease who have leukemia are more prone to Anthracycline-associated cardiotoxicity compared to those with Down syndrome and structurally healthy hearts.

### AUTHOR CONTRIBUTION

Conception & designs: N E, A H & M M. Data Collection: M M, H A. & M. Interpretation of data was done by all authors. All authors gave final approval & contribution to the writing of the final manuscript. ALL authors meet the ICMJE authorship criteria.

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### **CONFLICT OF INTEREST**

We declared no conflict of interest.

### FUNDING

The study has no funding or financial support.

### AVAILABILITY OF DATA AND MATERIALS

The datasets used/analyzed during this study are available from the corresponding author on request.

# ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The Institutional Review Board (IRB) of the National Cancer Institute, Cairo University, accepted the waiver of the patient consent form because the study was retrospective, used archival data, and had no impact on patient well-being. Patient confidentiality was always respected in compliance with National Cancer Institute and Cairo University rules. Data collection and presentation were conducted anonymously, and privacy and confidentiality were maintained to the greatest feasible levels.

### **POSSIBLE RISK**

No additional risk was added as it is a retrospective study.

### CONSENT FOR PUBLICATION

All patients (guardians/parents) have acceptance and consent to publish their data. All personal information has been made anonymous.

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