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ORIGINAL ARTICLE

Adrenal crises in children with adrenal insufficiency: epidemiology and risk factors

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Abstract

The aim of the study was to assess the epidemiology and risk factors of adrenal crises (AC) in children with adrenal insufficiency (AI). Children diagnosed with AI between 1990 and 2017 at four Israeli pediatric endocrinology units were studied. Demographic and clinical data were retrieved retrospectively from their files. The study population consisted of 120 children (73 boys, 47 girls) and comprised 904 patient years. Median age at diagnosis was 0.3 years (0–17.5). Thirty-one AC events in 26 children occurred during the study period, accounting for a frequency of 3.4 crises/100 patient years. Fifty-two percent of AC events occurred at presentation. The significant risk factors for developing AC were the following: younger age at diagnosis ($P = 0.003$), primary AI vs. secondary AI ($P = 0.016$), specific diagnosis of autoimmune AI, adrenal hypoplasia congenita and salt wasting congenital adrenal hyperplasia ($P < 0.001$), mineralocorticoid treatment ($P < 0.001$), and recurrent hospital admissions ($P > 0.001$). After applying a stepwise logistic regression model, only the group of diagnoses, including salt wasting CAH, AHC, and Addison's disease, remained significant predictor of AC (OR 17.5, 95% CI 4.7–64.9, $P < 0.001$). There was no AC-associated mortality during the study period.

Conclusions: Since significant percent of AC events occurred at presentation, measures to increase the awareness to signs and symptoms of AI among primary care physicians should be taken. Efforts to prevent AC should be focused on younger patients, especially those with primary AI.

What Is Known:
- *Diagnosis and long-term management of pediatric patients with adrenal insufficiency (AI) remain a challenge.*
- *Adrenal crises (AC) pose life-threatening emergencies in affected youngsters. Studies on the rate and risk factors of AC in children with AI are scarce, and they were done mainly on children with congenital adrenal hyperplasia (CAH).*

What Is New:
- *The rate of AC was relatively low and there was no AC-associated mortality during the study period.*
- *Children with primary AI were at higher risk for AC than children with secondary AI. Specifically, children with salt wasting CAH, adrenal hypoplasia congenita, and Addison's disease at the highest risk.*

Keywords Pediatric · Epidemiology · Adrenal insufficiency · Adrenal crisis

Abbreviations

AC Adrenal crises
ACTH Adrenocorticotrophic hormone
AHC Adrenal hypoplasia congenita

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AI	Adrenal insufficiency
ALD	Adrenoleukodystrophy
CAH	Congenital adrenal hyperplasia
CI	Confidence interval
OR	Odds ratio

Introduction

Adrenal insufficiency (AI) results from dysfunction of the adrenal gland cortex, leading to impaired secretion of glucocorticoids with or without mineralocorticoid deficiency [1–3]. It can be primary due to adrenal gland malfunction, or secondary due to lack or suppression of adrenocorticotrophic hormone (ACTH) secretion [4]. Primary AI in children can be congenital or acquired. Causes of congenital AI include (1) enzymatic defect in the cortisol and aldosterone synthesis (congenital adrenal hyperplasia [CAH]), the most common cause of which is 21-hydroxlase deficiency; (2) adrenal hypoplasia congenita (AHC); (3) component of autoimmune poly glandular syndrome type 1 secondary to autoimmune regulatory gene *AIRE* mutation; and (4) adrenoleukodystrophy (ALD). The most common acquired cause is autoimmune adrenalitis (Addison's disease) [1, 2]. Secondary AI can be congenital and either part of multiple pituitary hormone deficiency or isolated ACTH deficiency secondary to *TPIT* mutation or acquired secondary to pituitary-hypothalamic tumor, trauma, infection, infiltration, or irradiation [5–7]. Presenting symptoms and signs of AI are often nonspecific and include fatigue, anorexia, nausea, emesis, abdominal pain, and weight loss, therefore, often delaying the diagnosis [1, 3, 8–10]. More specific signs and symptoms include hyperpigmentation and salt craving (in primary AI), as well as postural hypotension, but they are not always present and are often misinterpreted or ignored. Laboratory finding may include hyponatremia, hypoglycemia, hyperkalemia, and metabolic acidosis [1–3, 8, 11].

Screening tests for AI include morning cortisol and ACTH levels and plasma renin activity [1, 3, 5]. The diagnosis is confirmed by the standard (250 microgram/m^2, maximum dose 250 microgram) ACTH test. A peak response of < 500–550 nmol/L (18–20 μg/dl) confirms the diagnosis [1, 3, 12, 13]. Some have advocated the use of low-dose ACTH test (1 mcg/m^2) for the diagnosis of secondary AI, but we and others have shown that both tests have similar diagnostic performance [14–16].

The treatment for AI consists of glucocorticoid replacement therapy [1, 3–6]. Patients with primary AI might also need mineralocorticoid replacement therapy (fludrocortisone acetate) [17]. The treatment for children mainly involves the administration of short-acting glucocorticoids, such as hydrocortisone, at a physiologic dose in order to prevent the growth suppression related to the long-acting glucocorticoids [11, 18]. Glucocorticoid dosage adjustment is required during stress conditions due to increased cortisol requirements [1, 3, 9].

Adrenal crises (AC) pose life-threatening emergencies that may occur in patients with AI, either at presentation due to delay in diagnosis or under appropriate steroid replacement therapy due to coexisting illness or non-compliance [19–24]. Studies on the rate of AC in children with AI are scarce [2, 23], and they were done mainly on children with CAH [25–28]. More data on the epidemiology and risk factors of AC events in childhood are needed in order to minimize their occurrence [23]. We therefore aimed to assess the incidence of AC and mortality rate in children with AI and to evaluate the risk factors for their development.

Materials and methods

Study population

The study included children and adolescents (age at diagnosis below 18 years) diagnosed with AI between 1990 and 2017 at four pediatric endocrinology units in Israel (Tel-Aviv Medical Center, Assaf Harofeh Medical Center, Kaplan Medical Center, and Wolfson Medical Center). The hospitals are located in three different regions of Israel. Three are secondary referral centers and one (Tel-Aviv Medical Center) is a tertiary referral center. Patients were recruited according to ICD-9-CM diagnosis (AI, CAH, Addison's disease, pituitary insufficiency, and hypopituitarism). Data were retrieved retrospectively from the patients' files, and they included demographic factors (age, sex, and ethnic origin), clinical information (age at diagnosis, specific diagnosis, clinical presentation, and family history), and details on therapy regimens (type, dosage, and parental guidance). Data on AC were retrieved according to ICD-9-CM diagnosis (AC, Addisonian crisis, or salt wasting crisis) and the patients' files. AC was defined as an acute clinical deterioration precipitated by a glucocorticoid-deficient state or rapid clinical improvement after administration of glucocorticoids with at least two of the following: severe fatigue, nausea and vomiting, somnolence, hypotension/sinus tachycardia relative to age-related norms, hyponatremia, hyperkalemia, or hypoglycemia [22–24].

Statistical analyses

Statistical analyses were performed using the BMDP program [29]. Descriptive statistics are given as mean and SD and/or median and range for continuous variables and frequency distribution for categorical variables. Comparison of different variables between subgroups was performed using one-way ANOVA and the Pearson chi-square test or Fisher's exact test as appropriate. We tested the equal variances using Levene's test. If the Levene's test findings were significant, we then

used the equality of means test (Welch or Brown-Forsythe). A pairwise *t* test was employed in order to examine this difference separately whenever there was a significant interaction. The incidence of AC was compared between children younger and older than 7 years. To identify predictors of an AC, we applied a stepwise logistic regression model with AC as a dependent variable and age at diagnosis, primary AI vs. secondary AI, mineralocorticoid treatment, and recurrent hospital admissions as independent variables. In addition, for the logistic regression, the diagnoses were divided into three groups: group 1 = simple virilizing CAH, group 2 = salt wasting CAH, AHC, and Addison's disease, and group 3 = secondary AI. Each group was included in the logistic regression as an independent variable. All tests were two-tailed, with significance taken at a threshold *P* value of < 0.05.

The study was approved by the medical ethics committee of each participating center.

Results

The study population consisted of 120 children (73 boys, 47 girls) and comprised 904 patient years. The children's median age at diagnosis was 0.25 years (range 0–17.5) and the median duration of follow-up was 7.4 years (range 0.6–18). Eighty-two children (68.3%) were diagnosed with primary AI 36 (44%) with simple virilizing CAH, 32 (39%) with salt wasting CAH, 8 (9.7%) with AHC, 5 (6.1%) with autoimmune adrenalitis (Addison's disease), and 1 (1.2%) with ALD. Thirty-eight (31.7%) patients had secondary AI, 21 (55.3%) with congenital hypopituitarism, and 17 (44.7%) with hypopituitarism secondary to brain neoplasms (Table 1). The hydrocortisone dosage was 12.3 ± 5.2 mg/m^2/day (13.1 ± 5.9 mg/m^2/day in the primary AI group and 9.2 ± 2.8 mg/m^2/day in the secondary AI group, $P < 0.001$). Sixty children (out of 82 patients with primary AI) also needed treatment with fludrocortisone at a mean dosage of 0.1 ± 0.04 mg/day.

Eighty-nine children (74.2%) were hospitalized during the study period, and 49 (40.8%) of them were hospitalized more than once. Overall, there were 186 hospitalizations (20.6 hospitalizations per 100 patient years), corresponding to a median of 1 (range 1–4) hospitalization per child. The causes for admissions were infections ($n = 63$, 33.9%), surgery ($n = 60$, 32.2%), noncompliance with treatment that did not end with AC ($n = 19$, 10.2%), AC ($n = 31$, 16.7%), and other causes ($n = 13$, 7%).

Thirty-one AC events occurred in 26 children during the study period, accounting for 3.4 AC cases per 100 patient years. Fifty-two percent of AC events occurred at presentation, 42% followed infection disease, and 6% were the result of noncompliance with treatment. The majority of the AC cases (92%) involved children younger than 7 years of age. The incidence of AC in that age group was 6.6 per 100 patient years. The frequency AC was significantly higher in children with primary AI compared to children with secondary AI (28% vs. 7.9%, $P = 0.016$) and in children with combined glucocorticoids and mineralocorticoid deficiency (i.e., salt wasting CAH, AHC, Addison's disease, and ALD) compared to children with only glucocorticoid deficiency (i.e., simple virilizing CAH and secondary AI 40% vs. 3.3%, $P < 0.001$). Twenty-two children had a single AC, three had two events and one had three events. Children who had AC at presentation were younger than children who did not (0.96 ± 2.35 vs. 3.92 ± 5.13 years, $P = 0.004$). Boys tended to have more AC compared to girls (27.4% vs. 12.8%, respectively, $P = 0.07$). After exclusion of X-linked causes of AI (i.e., ALD and AHC), the boys still had slightly more AC events than the girls, but this did not reach a level of significance (20.3% vs. 12.8%, respectively, $P = 0.31$). Girls with salt wasting CAH present with ambiguous genitalia while boys may present with AC. After exclusion of salt wasting CAH, AC was diagnosed in 16% of the boys and 13.8% of the girls ($P = 0.79$) (Table 2). Hyponatremia (sodium < 135 nmol/l) occurred in 27/30 events (90%), hyperkalemia (potassium > 5.5 mmol/l) in 16/30 (53%), and hypoglycemia (glucose < 60 mg/dl) in 12/25 events (48%), tachycardia in 8/19 (42%) events, and hypotension in 8/30 (27%) events. The clinical features of patients with AC are summarized in Table 3.

The risk factors for developing AC according to bivariate analysis were younger age at diagnosis ($P = 0.003$), primary compared to secondary AI ($P = 0.016$), specific diagnosis that included salt wasting CAH, AHC, Addison's disease, and ALD ($P < 0.001$), mineralocorticoid treatment ($P < 0.001$), and recurrent hospital admissions ($P > 0.001$).

Basal cortisol levels during ACTH testing at diagnosis tended to be lower in children who developed AC compared to children who did not (128 ± 121.61 vs. 183 ± 166.16 nmol/L, respectively, $P = 0.13$). Children who developed AC were treated with slightly and not significantly higher doses of hydrocortisone than those who did not (13.3 ± 4.8 vs. 12.0 ± 5.3 mg, respectively, $P = 0.25$). Among the children who had been treated with fludrocortisone, there was no significant difference in the dosages between those developed AC and those who did not (0.10 ± 0.05 vs. 0.09 ± 0.04 mg, respectively, $P = 0.46$).

The use of an emergency card or possession of a Solu-Cortef kit for self-injection (hydrocortisone sodium succinate ampoule for intramuscular or subcutaneous injection) was not associated with the development of AC. Eighty-seven percent (104/120) of the patients carried an emergency card and 47% (56/120) possessed an emergency kit. Among the children who did develop AC after diagnosis, 91% (10/11) carried an emergency card and 27% (3/11) also possessed a Solu-Cortef kit, compared to 86% (94/109) ($P = 0.99$) and 49% (53/109) ($P = 0.18$), respectively, for those that did not develop AC after diagnosis.

Table 1 Demographic, clinical, laboratory, and treatment characteristics of the study population

Clinical characteristics	Entire group ($n = 120$)	Females ($n = 47$; 39.2%)	Males ($n = 73$; 60.8%)	P
Age at diagnosis mean ± SD years	3.2 ± 4.8	2.2 ± 4.0	3.9 ± 5.1	0.04
AI diagnosis				0.24
Primary, *n*	82 (68.3%)	35	47	
Secondary, *n*	38 (31.7%)	12	26	
Specific AI diagnosis				0.005*
Primary				
Simple virilizing CAH, *n*	36 (44%)	19	17	
Salt wasting CAH, *n*	32 (39%)	18	14	
AHC, *n*	8 (9.7%)	0	8	
Addison's disease, *n*	5 (6.1%)	0	5	
ALD, *n*	1 (1.2%)	0	1	
Secondary				
Idiopathic/congenital, *n***	21 (55.3%)	7	14	
Brain tumor, *n*	17 (44.7%)	5	12	
ACTH test results				
Basal cortisol (nmol/L)	167.3 ± 155.7			
Peak cortisol (nmol/L)	284.2 ± 228.4			

* Due to gender difference for AHC, Addison's disease, and ALD

** 20 patients with multiple pituitary hormone deficiency and one with isolated ACTH deficiency (*TPIT* mutation)

AI adrenal insufficiency, *CAH* congenital adrenal hyperplasia, *AHC* adrenal hypoplasia congenita, *ALD* adrenoleukodystrophy

Applying a stepwise logistic regression model revealed that only the group of diagnoses including salt wasting CAH, AHC, and Addison's disease, remained significant predictor of AC (OR 17.5, 95% CI 4.7–64.9, $P < 0.001$).

Finally, there was no AC-associated mortality during the study period. However, there were five reports of a family history of pediatric AC-associated mortality. Specifically, four deaths occurred during infancy due to missed diagnosis (2 infants had AHC, 1 had salt wasting CAH, and 1 had isolated ACTH deficiency due to *TPIT* mutation). The fifth patient with AHC died at 5 years of age due to inappropriate glucocorticoid dose adjustment during a coexisting illness.

Discussion

AC is a life-threatening complication of AI. Although preventable, morbidity and mortality from AC are still unacceptably high [10, 24, 26, 30]. It is therefore essential to identify risk factors for the development of AC in order to apply preventive measures. According to the findings of our current study, the frequency of AC is 3.4 per 100 patient years, which is lower than the frequency of 7.2 per 100 patient years reported recently in children with CAH [31]. In another two studies on young children with CAH, the frequencies were 6.5 [27] and 10.9 [25] per 100 patient years. Indeed, when we computed the frequency of AC to children younger than 7 years of age, we also found a frequency of 6.6 per 100 patient years. Interestingly, studies on adult patients with AI found similar frequencies of between 5 and 10 AC per 100 patient years [19, 20, 22, 24, 31]. These findings from studies done over the last decade suggest that measures to prevent AC are still not sufficient.

We found that 52% of the AC occurred at presentation, similar to the 44% found in adults with primary AI [21] and to the 59% found in subjects with salt wasting CAH [32]. This high incidence could be due to lack of awareness of the diagnosis on the part of the primary care physicians. Adults with AI who developed AC were diagnosed later than those who did not develop AC (9 months compared to 6 months, respectively), and those who had previously been seen by an endocrinologist had a smaller risk to develop AC [21]. Therefore, greater efforts should be made to increase the awareness of primary care physicians to symptoms of AI due to its rarity and non-specific symptoms. A neonatal CAH screening program [33] was initiated in Israel in 2008. Our cohort of children with salt wasting CAH is too small to draw any conclusion regarding the impact of such a program on prevention of AC in that group.

Younger age at diagnosis was a risk factor for AC. We found a higher incidence of AC in infants, with 52% of the AC events having occurred in the first year of life. Similar to our results, studies on children with CAH [25, 26] found that the majority of AC also occurred in the young age group. Other studies [34, 35] on children with AI found that admission rates were highest among infants and that they decreased

Table 2 Demographic and clinical characteristics by AC

Variable	Children that developed AC ($n = 26$)	Children that did not develop AC ($n = 94$)	P
Age at diagnosis (year)	0.96 ± 2.35	3.92 ± 5.13	0.003
Gender			0.069
Male, *n*	20 (27.4%)	53 (72.6%)	
Female, *n*	6 (12.8%)	41 (87.2%)	
Gender (X-linked cases excluded)			0.31
Male, *n*	13 (20.3%)	51 (79.7%)	
Female, *n*	6 (12.8%)	41 (87.2%)	
Gender (X-linked and salt wasting CAH excluded)			
Male, *n*	8 (16.0%)	42 (84.0%)	0.79
Female, *n*	4 (13.8%)	25 (86.2%)	
AI diagnosis			0.016
Primary, *n*	23 (28%)	59 (72%)	
Secondary, *n*	3 (7.9%)	35 (92.1%)	
Specific AI diagnosis			< 0.001
AHC, ALD and Addison's disease, *n*	9 (64.3%)	5 (35.7%)	
Salt wasting CAH, *n*	12 (37.5%)	20 (62.5%)	
Simple virilizing CAH, *n*	2 (5.6%)	34 (94.4%)	
Secondary (idiopathic), *n*	3 (14.3%)	18 (85.7%)	
Secondary (tumor), *n*	0 (0%)	17 (100%)	
Hormones values at diagnosis (nmol/L)			
Basal cortisol, mean ± SD	128.18 ± 121.61	183.59 ± 166.16	0.13
Peak cortisol, mean ± SD	271.04 ± 255.96	289.9 ± 207.8	0.75
MC therapy needed, *n*	24 (92.3%)	2 (2.1%)	< 0.001
MC therapy dosage (mg)	0.1 ± 0.05	0.09 ± 0.04	0.46
HC therapy dosage (mg/m^2/day)	13.3 ± 4.8	11.9 ± 5.3	0.20
Hospital admissions, mean ± SD	2.34 ± 1.41	1.3 ± 1.35	< 0.001

AI adrenal insufficiency, *CAH* congenital adrenal hyperplasia, *AHC* adrenal hypoplasia congenita, *ALD* adrenoleukodystrophy

Table 3 Clinical and laboratory features of 31 episodes of adrenal crisis

Characteristic	Value mean ± SD
Systolic blood pressure (mmHg)	91 ± 20
Diastolic blood pressure (mmHg)	53 ± 16
Pulse (bpm)	125 ± 27
Sodium (mEq/L)	124.6 ± 7.7
Potassium (mEq/L)	6.2 ± 1.95
Glucose (mg/dL)	63.3 ± 36.8
White blood cells (K)	16.6 ± 11.6
Frequency of:	
Hyponatremia (< 135 mmol/L)	27/30 (90%)
Hyperkalemia (> 5 mmol/L)	16/30 (53%)
Hypoglycemia (< 60 mg/dL)	12/25 (48%)
Tachycardia	8/19 (42%)
Hypotension	8/30 (27%)

with age. This finding might be explained by the frequent coexisting infections in this age group.

Children with primary AI were at higher risk for AC than children with secondary AI. Those who also needed mineralocorticoid replacement had a significantly higher rate of AC than those who needed only glucocorticoid replacement. The significance of mineralocorticoid deficiency in addition to glucocorticoid deficiency as a risk factor for AC has been reported in previous studies [17, 20, 25, 27, 32, 36], and the findings emphasize the need for careful follow-up of the mineralocorticoid axis in subjects with primary AI [17, 19].

Under treatment with glucocorticoids [31, 37] or mineralocorticoids [17, 19] was suggested as a risk factor for the development of AC. However, in our study, the doses were similar between those patients who developed AC and those who did not.

Recurrent admissions were found to be a risk factor for the development of AC. A prospective study on adult patients

with AI [20] found that a history of former AC was a risk factor of future AC. It follows, therefore, that patients with recurrent admissions require more intensive preventive efforts. After diagnosis, the most frequent associated factor that led up to an AC event was infections (42%) and, to a lesser extent, non-compliance with treatment (6%). These findings are in concordance with previous studies on adults [20, 31, 32] and children [23, 25, 27, 28]. Notably, there is an overlap between symptoms of gastroenteritis and AC whereupon the diagnosis and initiation of therapy of AC can be delayed.

Basal cortisol levels at diagnosis tended to be lower in children who developed AC compared to children who did not. Similarly, in a study on adult with primary AI [21] basal cortisol levels were significantly lower in patients with AC compared to those without (54.5 nmol/L vs. 116.4, respectively). This finding suggests that more profound cortisol deficiency is a risk factor for AC.

The most common laboratory feature of AC was hyponatremia occurring in 90% of the cases followed by hyperkalemia (53%) and hypoglycemia (48%). This finding is similar to previous studies on children [2] and adults [21] with primary AI and on young children with CAH [25, 27, 28]. This finding is in concordance to our finding that a requirement for mineralocorticoid replacement therapy is a significant risk factor for AC.

Interestingly, the preventive measures of carrying emergency card or a possession of an emergency kit did not arrest the development of AC as reported by others [28]. In our cohort, 87% (104/120) of the patients carried an emergency card and 47% (56/120) possessed an emergency kit (due to the chart review nature of our study we cannot know how many of them used it when needed). A recent study [38] found that only 2/3 of the patients with AI possessed an emergency kit and only 60% of them felt secure about using it. A prospective study on adult patients with AI [20] found that whereas all patients carried an emergency card, provision with emergency kit was missing in most patients. Other studies on adults [19] and children [28] reported that only 12% and 22%, respectively, used an emergency kit during acute illness. These findings suggest that repeated education and practicing the use of emergency kit by the patients or their parents is needed.

Although adrenal insufficiency is a treatable disease, failure to recognize an adrenal crisis and institute appropriate and timely intervention has led to preventable deaths [20, 24, 39]. In the current study, the rate of AC was relatively low and no case ended in mortality. In a retrospective study on children with CAH [35] conducted over a similar period of our study, there were also no deaths recorded. In contrast, AC-associated mortality was reported in adults [20, 24] during the same period with a mortality rate of 0.5 per 100 patient years. The lack of mortality in our cohort can be explained by the proximity of the patients in central Israel to an emergency room and availability of 24/7 on call endocrine service in all participating centers.

Our cohort having included more boys than girls (73 vs. 47, respectively) cannot be explained solely by X-linked causes ($n = 9$) of AI. The gender difference is due to the fact that all Addison's disease cases ($n = 5$) were boys and more boys than girls had secondary AI. While we have no explanation for the gender difference in either Addison's disease or in congenital hypopituitarism, brain tumors are known to be more prevalent in males, which can explain the gender difference in secondary AI due to tumor [34, 40].

The strengths of the study were that the information was based on patients' charts and not on their self-reports, and that it included patients with both primary and secondary AI. In addition, this is a multi-center study from different regions of the country over a long follow-up period with a significant number of patient years. The limitations of the study are its retrospective nature and that we are not certain whether the participating centers represent all health services in Israel.

In summary, diagnosis and long-term management of patients with adrenal insufficiency remains a challenge. Since significant percent of AC events occurred at presentation, measures to increase the awareness to signs and symptoms of AI among primary care physicians are paramount importance. Efforts to prevent AC should be focused in younger patients, especially those with primary AI with both glucoco-and mineralo-corticoid deficiencies.

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YL: Data collection and analysis, literature search
AO: Study design, data analysis, and interpretation
AZ, MR, ASD, and ASB: Data collection, analysis, and interpretation
All authors were involved in the preparation of the manuscript, critically reviewed the manuscript, and approved the final manuscript as submitted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent This study was approved by the medical ethics committee of each participating center; the requirement for informed consent was waived.

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