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Prevalence and clinical features of severe diabetic ketoacidosis treated in pediatric intensive care unit: a 5-year monocentric experience

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Abstract

Background Diabetic ketoacidosis (DKA) is one of the most alarming concerns in the management of type 1 diabetes (T1D) in pediatric age. Prevalence of DKA at the onset of diabetes ranges from 30 to 40%. In selected cases of severe DKA, admission to pediatric intensive care unit (PICU) should be considered.

Methods This study aims to assess the prevalence of severe DKA treated in PICU in our 5-year monocentric experience. Secondary outcome of the study was to describe the main demographical and clinical features of individuals who required admission to PICU. All clinical data were collected by retrospectively reviewing the electronic medical records of children and adolescents with diabetes hospitalized in our University Hospital from January 2017 to December 2022.

Results During the study period, 103 children and adolescents were newly diagnosed with T1D. Among these, 51.5% presented clinical criteria for DKA and almost 10% needed to be treated in PICU. A higher rate of new T1D diagnoses was observed in 2021, as well as episodes of severe DKA being more frequent than in previous years. Due to severe clinical manifestations of DKA, 10 subjects (9.7%) with T1D onset needed to be treated in PICU. Of these, four children were younger than 5. The great majority came from a low household income and some of them had also immigrant background. The most common complication of DKA was acute kidney injury presented by four children. Other complications were cerebral edema, papilledema and acute esophageal necrosis. A 15-year-old girl had deep vein thrombosis (DVT) that evolved into multiple organ failure leading to death.

Conclusions Our findings demonstrated that severe DKA is still quite common in children and adolescents at T1D onset, especially in some areas such as Southern Italy. Public awareness campaigns should be increasingly promoted to facilitate the recognition of early symptoms of diabetes and to reduce morbidity and mortality related to DKA.

Keywords Acute kidney injury, Bicarbonate, Cerebral edema, Children, Deep vein thrombosis, Glasgow Coma Scale, Immigrant background, Type 1 diabetes

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Background

Diabetic ketoacidosis (DKA) is the major cause of morbidity and mortality in children with type 1 diabetes (T1D). It can occur in previously undiagnosed individuals with diabetes or may be secondary to omission of insulin injections, insulin pump failure, or inadequate management of an infection. Prevalence of DKA at the onset of T1D ranges from 30 to 40% in high-income countries [1, 2]. DKA is caused by absolute or relative insulin deficiency and high counterregulatory hormone concentrations, which accelerate catabolic state with increased glucose production via glycogenolysis and gluconeogenesis and impaired peripheral glucose utilization, resulting in hyperglycemia and hyperosmolality. Insulin deficiency and increased counterregulatory hormone levels also cause lipolysis and accumulation of ketones leading to ketonemia and metabolic acidosis [3]. According to the consensus statement from the International Society for Pediatric and Adolescent Diabetes (ISPAD) [4], DKA is defined by the presence of the following biochemical signs: blood sugar > 200 mg/dl (11 mmol/L), venous pH < 7.3 or serum bicarbonate < 18 mmol/L, beta-hydroxybutyrate > 3 mmol/L or moderate—large urine ketones. The severity of DKA is determined by the degree of acidosis: mild (pH < 7.3 or serum bicarbonate < 18 mmol/L), moderate (pH < 7.2 serum bicarbonate < 10 mmol/L), severe (pH 7.1, serum bicarbonate < 5 mmol/L). DKA therapy aims at correcting acidosis, hyperketonemia, dehydration, and dyselectrolytemia if present, along with a gradual normalization of serum glucose values. Mortality rates for DKA in Western countries range from 0.15 to 0.31% [5]. The most insidious complication of DKA is cerebral edema (CE), which occurs in 0.3—1% of cases and is fatal in 20—30% of cases [6]. Admission to pediatric intensive care unit (PICU) should be considered for individuals with several risk factors for CE (i.e. pre-school age, severe acidosis, elevated blood urea nitrogen, low partial carbon dioxide pressure), and for all those with severe DKA characterized by depressed level of consciousness, impaired circulation, and long duration of symptoms [4].

Methods

Aim of this retrospective study was to assess the prevalence of severe DKA treated in PICU in our monocentric experience both among new diagnosis of T1D and among secondary DKA cases. Secondary outcome of the study was to describe the main demographical and clinical features of individuals who required admission to PICU. We selected children and adolescents admitted to our tertiary-care center between January 2017 and December 2021 with a new diagnosis of T1D. Our University Hospital, set in the metropolitan city of Messina, includes both a regional reference center for pediatric diabetes and a PICU. Children and adolescents up to 16 years with newly diagnosed T1D from eastern Sicily and from the nearby province of Reggio Calabria, in the Calabria region, are regularly admitted to our facility. Our territorial prevention strategies for DKA include the identification of subjects at risk based on the presence of a first-degree relative with known T1D and public awareness campaigns in schools. The study was conducted in compliance with the Helsinki Declaration, good clinical practice and all applicable laws and regulations. Our investigation was not subject to ethical committee approval since it was limited to anonymized and unidentifiable data routinely collected in our clinical practice. The diagnosis of DKA was made according to the latest ISPAD Clinical Practice Consensus Guidelines [7].

Demographic and socioeconomic information including gender, age, family history of T1D, immigration background, family income, and clinical data such as anthropometric parameters, venous pH, serum bicarbonate levels, glycated hemoglobin (HbA1c) values, diabetes-specific autoantibody profiles, and clinical outcomes were collected. Regarding individuals admitted to PICU with severe DKA, further biochemical data including blood glucose, ketonemia, blood urea nitrogen (BUN), serum creatinine, serum potassium, and c-peptide levels were considered. Clinical features at the time of PICU admission, type of DKA treatment, and eventual occurrence of complications were also recorded. Cases of acute kidney injury (AKI) were defined according to Kidney Disease Improving Global Outcomes guidelines by an increase of at least 1.5 times the estimated baseline of serum creatinine [8].

Descriptive statistics were performed, and results are expressed using frequencies and percentages for qualitative variables, median and interquartile ranges for quantitative variables. A post-hoc subgroup analysis was made to compare clinical data between different subgroups of individuals newly diagnosed with T1D according to the severity of DKA at the onset of disease. ANOVA test was applied for quantitative parameters and $\chi 2$ test or Fisher's exact test, when appropriate, was used for categorical variables. Statistical significance level was set at $p < 0.05$.

Results

During the study period, 103 children and adolescents (62.1% males) with median age 9.5 years (6.5; 12.3) were newly diagnosed with T1D. Among these, 53 (51.5%) presented clinical criteria for DKA, of which 19 (18.4%) had severe DKA. A higher rate of new T1D diagnoses, especially during warm months, was observed in 2021, as well as cases of severe DKA being more frequent than in previous years (Figs. 1 and 2). Demographic,

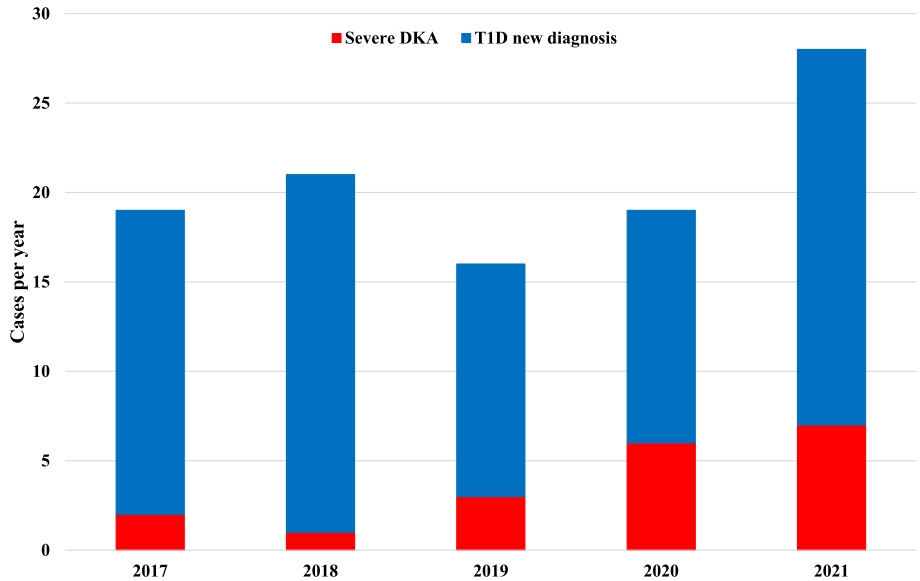

Fig. 1 New cases of T1D and hospitalizations for severe DKA over the period 2017–2021

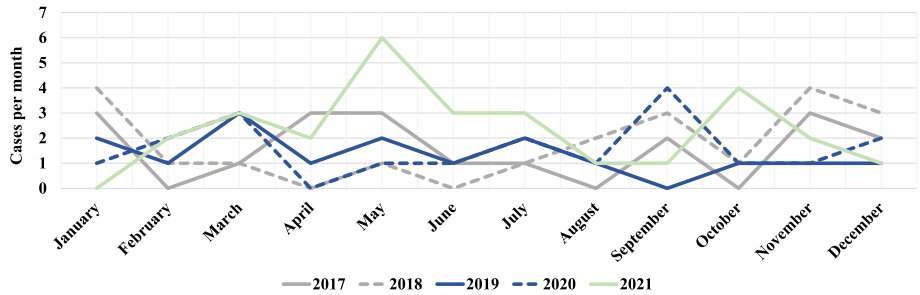

Fig. 2 Seasonality of new cases of T1D over the study period

socioeconomic, clinical characteristics of subjects with T1D onset, and comparison between groups according the severity of DKA are summarized in Table 1.

Patients admitted to PICU

Due to severe clinical manifestations of DKA, 10 individuals (9.7%) with T1D onset needed to be treated in PICU. Their demographic and clinical features are shown in Table 2. Seven of them (70%) were male, and age ranged from 1.0 to 14.9 years. Four children were younger than 5. The majority came from a low household income (<€15.000), and almost half of them (40%) came from an immigrant background. None of them had a first-degree relative with T1D. Median blood glucose at admission was 525 mg/dl (449; 710), while HbA1c was 10.9% (10.2; 12.6). Basal c-peptide levels were < 0.8 ng/mL in most individuals, and T1D-specific autoimmunity was absent in only one child. Polyuria, polydipsia, Kussmaul's breathing and gastrointestinal symptoms (i.e. abdominal pain, vomiting) were equally distributed among individuals as presenting symptoms. Half of the subjects presented with severe neurological impairment (Glasgow coma scale < 9), while four (40%) had a Glasgow coma scale between 9 and 13. At PICU admission, median venous pH was 6.88 (6.84; 6.94), serum bicarbonate level was 5 mmol/L (3.3; 5.7), and ketonemia was 5.5 mmol/L (4.5; 6.3). Abnormal levels of potassium before the start of DKA correction were found in only one child, who presented hyperkalemia. Fluid replacement and intravenous insulin administration was practiced for a median period of 40.5 h (31.5; 66), while bicarbonate therapy was required in three cases. The most common complication of DKA was AKI presented by four individuals. Signs of papilledema were found in one boy and an overt condition of CE was diagnosed in another subject. A 1-year-old child experienced black esophagus. Finally, a 15-year-old girl had deep vein thrombosis (DVT) that evolved to multiple organ failure resulting in death.

Table 1 Clinical features of new cases of type 1 diabetes during the study period and comparison between subgroups according to the severity of diabetic ketoacidosis

	No DKA	Mild DKA	Moderate DKA	Severe DKA	*p* value
Number of patients	50 (48.5%)	25 (24.3%)	9 (8.7%)	19 (18.4%)	
Age (years)	10.3 (6.7; 12.3)	9.1 (7.2; 12.1)	9.8 (8.7; 13)	6.0 (1.9; 11.5)	0.019*
Gender					0.122
Male	30 (60%)	18 (72%)	6 (66.7%)	10 (52.6%)	
Female	20 (40%)	7 (28%)	3 (33.3%)	9 (47.4%)	
Height (Z-score)	0.49 (-0.72; 0.90)	-0.03 (-0.39; 0.81)	-0.56 (-1.08; -0.28)	-0.49 (-0.92; 0.55)	0.374
Weight (Z-score)	-0.06 (-0.59; 0.81)	-0.35 (-1.05; 1.11)	-0.04 (-0.58; 0.1)	-0.26 (-0.92; 0.77)	0.827
BMI (Z-score)	0.52 (-0.44; 1.62)	0.36 (-0.77; 1.96)	0.51 (-0.06; 1.00)	-0.14 (-0.82; 0.95)	0.465
Family history of T1D (1st degree)	6 (12%)	2 (8%)	1 (11.1%)	0	n.a
Low household income	23 (46%)	12 (48%)	4 (44.4%)	11 (57.9%)	0.279
Immigrant background	3 (6%)	0	0	5 (26.3%)	n.a
Venous pH	7.35 (7.33; 7.38)	7.27 (7.24; 7.29)	7.14 (7.14; 7.2)	6.91 (6.85; 7.00)	< 0.001*
Serum bicarbonate (mmol/L)	21.4 (20.1; 22.9)	16.2 (14.7; 18.2)	10.7 (10.6; 11.1)	6.5 (5.1; 7.7)	< 0.001*
HbA1c at onset (%)	11.2 (8.9; 13.7)	11.9 (9.6; 13.4)	12.4 (11.3; 14)	11.1 (10.7; 12.6)	0.874
T1D autoantibodies	35 (70%)	21 (84%)	6 (66.7%)	14 (73.7%)	0.741
Cerebral edema	0	0	0	1 (5.3%)	n.a
Mortality	0	0	0	1 (5.3%)	n.a

BMI Body mass index, *DKA* Diabetic ketoacidosis, *HbA1c* Glycated hemoglobin, *n.a* Not available *T1D* Type 1 diabetes

* significant *p*-value

Secondary DKA

Additionally, 7 individuals already diagnosed with T1D presented were hospitalized due to secondary DKA during the entire study period. Of these, two (28.5%) needed to be treated in PICU. Both subjects came from an immigrant and low household income background. In the first case of an adolescent female on multiple daily injection insulin therapy, secondary DKA was caused by bad therapeutic management characterized by recurrent omission of insulin administrations for several days. In the other case, a 6-year-old female child was forced to discontinue insulin therapy for a long time due to adverse circumstances related to a clandestine migration journey. DKA was complicated by the occurrence of AKI, CE, and multiple organ failure but without chronic sequelae (Table 3).

Discussion

Our single-center 5-year experience revealed that prevalence of DKA at T1D onset was 51.5% and almost 10% of young individuals newly diagnosed with T1D needed to be treated in PICU. Despite numerous public health campaigns being promoted in several countries to increase awareness and knowledge about pediatric diabetes during the past years [9–11], initial symptoms of T1D are often overlooked, and DKA is still common among children and adolescents [12]. However, frequency of DKA greatly varies between different areas, with lower rates in areas such as the Sardinia region, Northern Europe and Canada, where populations are likely more sensitized about the risk of T1D due to high incidence rates of the disease [13].

Interestingly, prevalence of severe DKA in our center was relatively higher in comparison to other Italian studies [14] and to other developed countries [15–17], but in accordance with recent epidemiologic data from Southern Italy [18, 19]. Our analysis also showed an apparent increase in severity of DKA during the period 2020–2021. This trend may be consistent with other studies [20–23], which attribute delays of T1D diagnosis and subsequent more severe presentation to indirect effects of the COVID-19 pandemic, such as the interruption of some outpatient services or omission of medical consultations due to fear of contracting SARS-CoV-2 infection by families. In accordance with our experience, a modification of the seasonality of T1D incidence rate during the pandemic years, with unprecedented peaks during warm months, has been observed in several countries [24]. This finding can be attributable to social distancing measures that may have altered the diffusion of epidemic viruses known to act as environmental triggers for the development of T1D. A direct effect of SARS-CoV-2 against β-cells through the binding to ACE2 receptors expressed in pancreatic tissue is currently under investigation [25].

Few studies reported data on rates of hospitalizations in PICU at T1D onset. Our prevalence of PICU admission due to severe DKA is lower than that found by a

Table 2 Summary of demographic, clinical and biochemical data of patients newly diagnosed with type 1 diabetes who required admission to pediatric intensive care unit due to severe diabetic ketoacidosis. Qualitative data are expressed by using frequencies and percentages, numerical data are indicated as median and interquartile ranges

Number of patients	10
Age (years)	5.6 (2.7; 8)
Gender	
Male	7 (70%)
Female	3 (30%)
Height (Z-score)	0.34 (-0.83; 1.34)
Weight (Z-score)	0.82 (-0.15; 0.93)
BMI (Z-score)	0.24 (-0.32; 1.10)
Family history of T1D (1st degree)	0
Low household income	8 (80%)
Immigrant background	4 (40%)
Clinical presentation	
Kussmaul's breathing	7 (70%)
Polyuria and polydipsia	7 (70%)
Gastrointestinal symptoms	7 (70%)
Severe neurological impairment (GCS < 9)	5 (50%)
Moderate neurological impairment (GCS between 9 and 13)	4 (40%)
Biochemical data	
Blood glucose at admission (mg/dl)	525 (449; 710)
Venous pH	6.88 (6.84; 6.94)
Serum bicarbonate (mmol/L)	5 (3.3; 5.7)
Base excess (mmol/L)	-28.4 (-30.2; -25.6)
Ketonemia (mmol/L)	5.5 (4.5; 6.3)
BUN (mg/dl)	27.5 (23; 34.2)
Serum creatinine (mg/dl)	0.6 (0.6; 0.9)
Serum potassium (mg/dl)	3.9 (3.4; 4.7)
HbA1c at onset (%)	10.9 (10.2; 12.6)
Autoantibodies	9 (90%)
Basal C-peptide (ng/ml)	0.26 (0.05; 0.4)
DKA treatment	
Duration of DKA treatment (hours)	40.5 (31.5; 66)
Bicarbonate administration	3 (30%)
Outcomes	
Acute kidney injury	4 (40%)
Cerebral edema	1 (10%)
MOF	1 (10%)
Other complications	1 (10%)
Mortality	1 (10%)

BMI Body mass index, *BUN* Blood urea nitrogen, *DKA* Diabetic ketoacidosis, *GCS* Glasgow coma scale, *HbA1c* Glycated hemoglobin, *MOF* Multiple organ failure, *PICU* Pediatric intensive care unit, *T1D* Type 1 diabetes

recent single-center study from Croatia [26]. Differences between rates of DKA-related hospitalizations in pediatric critical care areas may be related to disparities in territorial availability of PICU or to different levels of expertise on DKA management in pediatric non-intensive units.

Severity of DKA presentation may be influenced by several factors, including those related to socioeconomic background of subjects. Our data showed that a consistent number of children belonged to low socioeconomic status had severe DKA or required admission to PICU as already demonstrated by larger scale studies [14, 27]. Our findings revealed that also immigrant background and ethnic minority status have been associated to higher

Table 3 Demographic, clinical and biochemical data of two patients with already diagnosed type 1 diabetes admitted to pediatric intensive care unit for severe secondary diabetic ketoacidosis

	Patient 1	Patient 2
Age (years)	13.3	6.5
Gender	Female	Female
Height (Z-score)	-0.75	-1.46
Weight (Z-score)	-2.10	-2.30
BMI (Z-score)	-1.96	-1.94
Family history of T1D (1st degree)	No	Unknown
Low household income	Yes	Yes
Immigrant background	Yes	Yes
Clinical presentation		
Kussmaul's breathing	Yes	Yes
Polyuria and polydipsia	Yes	No
Gastrointestinal symptoms	Yes	No
Severe neurological impairment (GCS < 9)	No	Yes
Moderate neurological impairment (GCS between 9 and 13)	No	No
Biochemical data		
Blood glucose at admission (mg/dl)	750	698
Venous pH	6.80	6.83
Serum bicarbonate (mmol/L)	5.6	3.0
Base excess (mmol/L)	-31	Unknown
BUN (mg/dl)	74	109
Serum creatinine (mg/dl)	1.3	1.2
Serum potassium (mg/dl)	6.2	3.4
HbA1c (%)	8.1	7.6
DKA treatment		
Duration of DKA treatment (hours)	96	48
Bicarbonate administration	No	No
Outcomes		
Acute kidney injury	No	Yes
Cerebral edema	No	Yes
MOF	No	Yes
Mortality	No	No

BMI Body mass index, *BUN* Blood urea nitrogen, *DKA* Diabetic ketoacidosis, *GCS* Glasgow coma scale, *HbA1c* Glycated hemoglobin, *MOF* Multiple organ failure, *PICU* Pediatric intensive care unit, *T1D* Type 1 diabetes

likelihood of developing severe DKA at T1D onset, as a result of language and cultural barriers that may hamper the awareness of the disease and delay the access to healthcare structures [14, 28, 29].

Our results confirmed that pre-school age remains a notable risk factor for developing severe DKA [18, 28]. The main hypothesis to explain the more severe metabolic decompensation in younger children is that the process of pancreatic beta cell destruction seems to be faster and more aggressive due to the activation of the pro-inflammatory cytokine storm [30, 31]. In addition, early symptoms of hyperglycemia are usually poorly recognized in this age group [32].

The use of bicarbonate to counteract the state of acidosis in children and adolescents with DKA has been widely discouraged by clinical evidence [33], due to the increased risk of harmful complications such as CE and hypokalemia. However, international DKA guidelines suggest the administration of bicarbonate in selected cases, including severe hyperkalemia or extreme acidosis that may compromise cardiac function [4]. In our experience, the use of sodium bicarbonate was restricted to those subjects with persistence of severe acidosis after more than 48 h of DKA correction, despite the normalization of blood ketones and glucose levels.

AKI is one of the most frequently encountered ongoing complications of severe DKA and is generally related to decreased renal perfusion caused by intravascular volume depletion [34]. In our experience, AKI was found in 40% individuals admitted in PICU and in 8.9% of total DKA cases. These findings are in line with data previously reported by other studies [35–37]. No evidence of further sequelae during the follow-up was found in our records. CE is the most alarming complication of DKA and the leading cause of mortality [38]. Some authors have hypothesized that cerebral hypoperfusion and reperfusion effects associated with neuroinflammation play a key role in the occurrence of CE [6, 39, 40]. Prolonged duration of DKA, severity of dehydration and acidosis, persistent hyponatremia, hypocapnia and bicarbonate therapy are factors that may facilitate the development of CE [41–43]. About 20–30% of CE survivors have residual disabilities ranging from mild neurological impairment to a vegetative state [44, 45]. In our study, only one case of cerebral edema was detected without any neurological sequelae.

In our study cohort, an interesting case of acute esophageal necrosis (AEN), also known as Gurvits syndrome or black esophagus, was present. AEN is an extremely rare condition characterized by necrotic lesions of esophageal mucosal and submucosal layers as the result of a combination of tissue hypoperfusion, impaired local defense barriers and massive influx of gastric contents [46–48]. Gastrointestinal bleeding is the most frequent clinical manifestation, often associated with early signs of hemodynamic instability [49].

Overall mortality in children with DKA ranges from 0.15 to 0.35% in Western countries such as the UK, Canada, USA and increases to 3.4—13.4% in low-middle income countries [5, 50]. In our study, only one individual died. The cause of death was multi organ failure secondary to DVT, which is a rare complication in children and adolescents. Shock and dehydration are the main causes for the state of hypercoagulability, which is the trigger of the coagulative cascade and venous stasis. The presence of femoral venous cannulation increases the risk of developing DVT [51].

The occurrence of DKA in subjects with already known T1D represents a major concern in clinical practice. In our experience, it was often characterized by severe presentation and required hospitalization in PICU in almost one third of cases. The most common causes of recurrent DKA are accidental or deliberate insulin omission, inadequate management of sick days, and unnoticed insulin pump failure. Support of clinical psychologists and a proper therapeutic education are crucial in the prevention of these events [4].

Conclusions

Severe DKA is still quite common in children and adolescents at T1D onset, especially in some areas such as Southern Italy. In a consistent number of cases, individuals with severe DKA need PICU treatment for the occurrence of life-threatening clinical manifestations, including impairment of vital functions and multiple organ failure. Our study highlights the need to increasingly promote public awareness campaigns to facilitate the recognition of early symptoms of diabetes and to reduce morbidity and mortality related to DKA.

Abbreviations

AEN	Acute esophageal necrosis
AKI	Acute kidney injury
CE	Cerebral edema
DKA	Diabetic ketoacidosis
DVT	Deep vein thrombosis
HbA1c	Glycated hemoglobin
ISPAD	International Society for Pediatric and Adolescent Diabetes
PICU	Pediatric intensive care unit
T1D	Type 1 diabetes

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Authors' contributions

SP: writing – original draft preparation; GS: conceptualization; BB, PB, IR, MV and FC: data curation; EG and FL: writing – review and editing. The paper has been read and approved by all the authors and each author considers that the paper represents their honest work. The author(s) read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Helsinki Declaration, good clinical practice and all applicable laws and regulations. Written informed consent was obtained from a parent and/or legal guardian of all the study participants.
The study was exempt from ethical committee approval since it was confined to anonymized and unidentifiable data routinely collected in our clinical practice.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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