Abstract

Objectives: While global incidence rates (IR) of childhood diabetes are increasing, there is a notable lack of current information on the incidence of childhood-onset diabetes in Thailand. This study aims to illustrate the age-standardized IR and types of childhood diabetes using multicenter regional data in Northern Thailand from 2005 to 2022 and to assess the impact of the COVID-19 pandemic.

Methods: Data on newly diagnosed childhood diabetes were retrospectively collected between 2005 and 2016 and prospectively recorded for all incident cases between 2016 and 2022. The capture-recapture method was applied to estimate the completeness of ascertainment. The age-standardized IR of diabetes was calculated. The IR of diabetes and the prevalence/severity of DKA at onset were compared between the pre-pandemic and pandemic periods.

Results: Among 210 patients, type 1 diabetes (T1D) accounted for 56.2 %, type 2 diabetes (T2D) for 39 %, and other types for 4.8 %. The T1D age-standardized IR significantly increased from 0.30 in 2005 to 3.11/100,000 person/year in 2022, mirroring the T2D trend, which increased from 0.33 to 3.15/100,000 person/year. The average T1D age-standardized IR, including the prevalence/severity of DKA at diagnosis, did not significantly differ between the pre-pandemic and pandemic periods (2.11 vs. 2.36/100,000 person/year, p-value=0.67). However, the average T2D age-standardized IR significantly increased from 0.83 to 2.15/100,000 person/year during the pandemic (p-value=0.0057).

Conclusions: This study highlights an increased incidence of childhood T1D and T2D in Northern Thailand over a two-decade period. Notably, during the COVID-19 pandemic, the T1D incidence remained stable, while a significant rise in T2D incidence was observed.

Keywords: childhood diabetes; incidence of diabetes; COVID-19

Introduction

The incidence of type 1 diabetes (T1D) has been globally increasing [1–3], and this trend is also observed in Thailand. In 1984–1985, the incidence rate (IR) of T1D among children aged 0–15 years in Thailand was reported at a low rate of 0.2/100,000 person/year [4]. In subsequent years, however, there was a notable increase in T1D incidence. Between 1991 and 1997, IRs varied across regions with figures of 0.3 in the Northeast, 0.37 in the North, 0.52 in the South, and a substantially higher 1.65/100,000 person/year in Bangkok [4–7]. From 1996 to 2005, the T1D IRs were recorded at 0.62 in the Northeastern region and ranged from 0.1 to 0.3/100,000 person/year in the Southern area [8, 9]. Data from 2006 to 2014 indicated that T1D incidence remained relatively stable, with a rate of 0.39–0.64/100,000 person/year in Southern Thailand [8]. The most recent data from the International Diabetes Federation (IDF) Atlas, 10th edition, 2021, indicates an age-standardized T1D incidence rate of 1.0/100,000/year among children aged 0–14 years based on a 2011 study in

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Northeastern Thailand [1]. Additionally, the escalating prevalence of type 2 diabetes (T2D) in Thai children and adolescents, largely attributed to the rise in childhood obesity, has also been observed [10]. Notably, there are significant gaps in our understanding of the current incidence rates of newly diagnosed childhood T1D and T2D in Thailand.

Several factors may contribute to the rising incidence of childhood diabetes, such as obesity, gut microbiome, childhood diet, early life factors, exposure to chemicals, and viral infections [11], notably the SARS-Coronavirus-2 pandemic (COVID-19) [12]. The initial report of COVID-19 infection emerged in China in December 2019 and rapidly spread globally. On January 30, 2020, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC), followed by a pandemic declaration on March 11, 2020 [13]. In Thailand, the first confirmed COVID-19 infection occurred on January 13, 2020 [14], leading to a public health emergency state declaration by the Thai government [15]. Ongoing scrutiny exists regarding the potential link between COVID-19 and the development of T1D [16]. Previous research suggests that COVID-19 infection may be involved in the autoimmune development of pancreatic cells, as the virus carries epitopes similar to β-cells, which can trigger the release of self-antigens, ultimately leading to β-cell destruction [12]. Many studies have demonstrated an increase in childhood T1D cases during the COVID-19 pandemic, along with a higher incidence or frequency of severe diabetic ketoacidosis (DKA) than pre-pandemic [17–23]. However, the impact of this virus on T1D development, the incidence/prevalence of DKA, and its severity remain subjects of debate. Some studies have indicated no significant increase in the incidence of new-onset T1D or the incidence of DKA at diagnosis during the COVID-19 pandemic [24–26].

The objectives of this study were to illustrate the incidence and types of newly diagnosed childhood diabetes using multicenter regional data in Northern Thailand and to compare the incidences of diabetes and the severity of DKA at onset between the pre-pandemic and COVID-19 pandemic periods.

Research design and methods

Data collection

This study employed both retrospective and prospective cohort study approaches. The capture-recapture method was applied to estimate the completeness of ascertainment. Our study focused exclusively on children and adolescents under the age of 15 who had been newly diagnosed with diabetes. These individuals were primarily sourced from three tertiary referral centers situated in four provinces (Chiang Mai, Chiang Rai, Lamphun, and Mae Hong Son) and were registered in the Thai Type 1 Diabetes and Diabetes diagnosed before Age 30 years Registry, Care and Network (T1DDAR CN). This registry had retrospectively documented newly diagnosed diabetes cases from 2005 to 2016 and had consecutively maintained prospective registration of all incident cases since 2016 [27]. These individuals comprised our primary data sources. Additional cases were recaptured through both secondary and tertiary sources. The secondary source involved collecting data from all other government and private hospitals, totaling 72 hospitals. The tertiary source encompassed data collected from all schools (1,777 schools) located within the same provinces. This data collection was facilitated through a combination of mail and an online questionnaire. Patients who had been diagnosed with gestational diabetes or had underlying conditions that could affect blood sugar levels, such as Cushing’s syndrome, or were receiving medications such as steroids or tacrolimus were excluded from our study.

Clinical data, including the type of diabetes, age at diagnosis, gender, year of diagnosis, number of new cases each year, diabetes symptoms, duration of symptoms, prevalence, and severity of DKA at diagnosis, laboratory investigations, diabetes autoantibodies, length of hospital stay, and mortality were collected. Both diabetes autoantibodies and C-peptide levels were supported by the T1DDAR CN. The type of diabetes was clinically diagnosed by pediatric endocrinologists. The study involved computing both the crude and age-standardized annual IR of newly diagnosed childhood T1D and T2D. Additionally, it included a comparison of the incidence of diabetes and the severity at onset, such as DKA, between the pre-pandemic and pandemic COVID-19 periods.

This study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University (Research ID: PED-2565-08836) and by the Institutional Review Board of each participating center. It was granted an exemption from requiring written informed consent since this research involved no more than minimal risk to the participants.

Definitions

The criteria for newly diagnosed and the classification of diabetes were in accordance with the 2019 World Health
Organization (WHO) guideline [28] and were consistent with our previous T1DDAR CN publication [27]. T1D was diagnosed in patients who presented with acute symptoms, marked hyperglycemia with or without ketoacidosis, and required insulin therapy within the first year after diagnosis, indicating absolute insulin deficiency. T2D was considered in patients who exhibited signs of insulin resistance and did not require insulin therapy to control hyperglycemia within the first year of diagnosis, indicating preserved insulin secretion. Other specific types of diabetes, including monogenic diabetes and genetic syndromes associated with diabetes and others, were considered as previously published elsewhere [27].

DKA at diagnosis was identified based on the 2018 International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guideline [29]. Additionally, DKA was further classified into three categories: mild (venous pH 7.20–7.29, serum bicarbonate (HCO₃⁻) 10–14.9 mmol/L), moderate (venous pH 7.10–7.19, serum HCO₃⁻ 5–9.9 mmol/L), and severe (venous pH<7.10, HCO₃⁻<5 mmol/L) [29].

The pre-pandemic period was defined as spanning from January 1, 2017, to December 31, 2019, while the COVID-19 pandemic period covered January 1, 2020, to December 31, 2022.

Statistical analysis

The crude IR of newly diagnosed diabetes was calculated per 100,000 person/year. This calculation involved dividing the number of new cases per year by the total number of children under 15 years of age in Chiang Mai, Chiang Rai, Lamphun, and Mae Hong Son Provinces for the same year and multiplying the result by 100,000. The population data were obtained from the National Statistical Office of Thailand. Furthermore, the number of newly diagnosed diabetes cases was categorized into three age groups (0–4, 5–9, 10–14 years). The IR was standardized using the direct method, accounting for the age distribution of the world population [30]. Additionally, the cumulative age-standardized IRs were also calculated. One-way ANOVA was used to determine the trend of the age-standardized IR of childhood diabetes over time. For comparing the pre-pandemic and pandemic age-standardized IRs, confidence intervals based on the gamma distribution were used [31, 32]. Other statistical analyses were conducted using the Chi-square test or Fisher’s exact test for categorical variables and the t-test or Mann-Whitney U test for continuous variables using SPSS version 22.0. A p-value of less than 0.05 was considered statistically significant.

Results

Types of diabetes and the IR of newly diagnosed T1D and T2D

A total of 210 cases of newly diagnosed childhood diabetes were identified between 2005 and 2022 from primary sources. This count also included 17 patients identified from secondary sources (with a response rate of 23.27 %) and 27 patients identified from tertiary sources (a response rate of 19.10 %), reflecting the comprehensiveness of our referral system and network in T1DDAR CN. Among these cases, 56.2 % were classified as T1D, 39 % as T2D, and 4.8 % as other specific types of diabetes.

Among the 15 patients with other specific types of diabetes, three had maturity-onset diabetes of the young (MODY), one had neonatal diabetes, four had Prader–Willi syndrome (PWS), two had chromosomal disorders including Down syndrome and isodicentric chromosome 15 syndrome, two had NEUROG3-associated syndrome, one had immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, one had microcephalic osteodystrophic primordial short stature, and one had another type of diabetes.

The age-standardized IR of newly diagnosed childhood T1D significantly increased from 0.30 to 3.11/100,000 person/year between 2005 and 2022 ([95 % CI 0.42–3.42], p-value=0.008). Similarly, the age-standardized IR of T2D also significantly increased from 0.33 to 3.15 ([95 % CI 0.42–3.46], p-value=0.008) during the same period, as shown in Figure 1A and Table 1. Figure 1B illustrates the number of newly diagnosed cases of T1D and T2D from 2005 to 2022. For T1D, the average age-standardized IRs did not differ between the pre-pandemic and COVID-19 pandemic periods (2.11 vs. 2.36 [95 % CI 0.67–1.87], p-value=0.67). However, there was a significant increase in the average age-standardized IR of T2D from 0.83 during the pre-pandemic period to 2.15/100,000 person/year during the pandemic ([95 % CI 1.31–3.67], p-value=0.0057).

Age at diagnosis of T1D and T2D

The mean age at diagnosis for T1D was 9.6±3.7 years, with the youngest case diagnosed at the age of one year. Among T1D cases, the highest number of diagnoses occurred in the age group of 10 to <15 years, followed by the age group of 5 to <10 years.

In contrast, for T2D, the average age at diagnosis was 12.1±2.0 years, with the majority of T2D cases identified in
The youngest identified T2D case was 4.2 years old. Notably, in this exceptional case, the diagnosis of T2D was made based on several compelling factors, including achieving insulin independence within two weeks after initiating treatment, severe morbid obesity with a BMI of 35 kg/m² and a BMI standard deviation score (SDS) of +13.64, the presence of acanthosis nigricans, and the absence of a family history of diabetes in first-degree relatives. Additionally, this patient had an initial HbA₁c level of 10.5 % and was simultaneously diagnosed with a COVID-19 infection at the time of her diabetes diagnosis. Initially, insulin was prescribed and successfully tapered off within

Figure 1: The trends of annual age-standardized incidence rates (panel A) and the number (panel B) of newly diagnosed T1D and T2D from 2005 to 2022. (A) The trends of annual age-standardized incidence rates of newly diagnosed T1D and T2D from 2005 to 2022. (B) The number of newly diagnosed T1D and T2D from 2005 to 2022.
The incidence rate was expressed as/100,000 person/year. T1D, type 1 diabetes; T2D, type 2 diabetes; CI, confidence interval.

2 weeks after diagnosis. Her diabetes autoantibodies including anti-glutamic acid decarboxylase antibody (anti-GAD) and anti-insulinoma-associated protein 2 (antiIA2) were negative. She has maintained euglycemia with metformin alone as observed during the last follow-up visit at 7 months after the diagnosis.

Characteristics of newly diagnosed childhood diabetes in pre-pandemic and pandemic periods

Type 1 diabetes

The number of newly diagnosed T1D cases was 32 patients in the pre-pandemic period and 37 patients in the pandemic period. There were no significant differences in age at diagnosis, gender, duration of symptoms, length of hospital stay, and death. Additionally, anthropometric data, fasting plasma glucose, pH, serum HCO3, and serum Na levels were not significantly different between the two periods. The prevalence of DKA at diagnosis was not significantly different between the pre-pandemic and pandemic period (66.6 vs. 58.3%; p-value=0.50). The severity of DKA (mild, moderate, severe DKA) was also not significantly different between these two periods (p-value=0.285). However, the length of hospital stay was shorter during the pandemic period (Table 2).

Type 2 diabetes

The number of newly diagnosed childhood T2D patients was 13 in the pre-pandemic period and 33 in the pandemic. There were no differences in age at diagnosis, gender, duration of symptoms, length of hospital stay, and death. Additionally, anthropometric data, fasting plasma glucose, pH, serum HCO3, and serum Na levels were not significantly different between the two periods. The prevalence of DKA at onset (12.5 vs. 12.5%; p-value=1.00) and severity (mild, moderate, severe DKA) (p-value=0.172) were not significantly different between the two periods. Notably, moderate-severe DKA was not identified in the pre-pandemic period; however, it was diagnosed in 12.5% of cases in the pandemic period. The random plasma glucose levels were significantly higher during the pandemic (248.33 ± 76.95 vs. 434.91 ± 117.13 mg/dL; p-value=0.023) (Table 3).
Table 2: Characteristics of newly diagnosed childhood T1D in the pre-pandemic and pandemic periods.

<table>
<thead>
<tr>
<th></th>
<th>Pre-pandemic (32)</th>
<th>Pandemic (37)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis, years</strong></td>
<td>12.50 (1.0–14.0)</td>
<td>11.0 (1.83–14.9)</td>
<td>0.477</td>
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<td>(minimum - maximum)</td>
<td></td>
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<tr>
<td>Male, n (%)</td>
<td>13 (40.6 %)</td>
<td>21 (56.8 %)</td>
<td>0.273</td>
</tr>
<tr>
<td>Duration of symptoms, days</td>
<td>17.50</td>
<td>14.00</td>
<td>0.701</td>
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<tr>
<td>(5.00–90.0)</td>
<td>(7.00–30.0)</td>
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<tr>
<td>BMI SDS</td>
<td>-0.61 ± 1.49</td>
<td>-0.47 ± 2.16</td>
<td>0.764</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>2 (7.14)</td>
<td>5 (14.28)</td>
<td>0.37</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>375 (322–529)</td>
<td>322 (284–354)</td>
<td>0.193</td>
</tr>
<tr>
<td>Random plasma glucose, mg/dL</td>
<td>523 (437–733)</td>
<td>440 (380–537)</td>
<td>0.055</td>
</tr>
<tr>
<td>Prevalence of DKA, n (%)</td>
<td>18 (66.6 %)</td>
<td>21 (58.3 %)</td>
<td>0.500</td>
</tr>
<tr>
<td>Severity of DKA, n (%)</td>
<td></td>
<td></td>
<td>0.285</td>
</tr>
<tr>
<td>Mild</td>
<td>7 (25.9 %)</td>
<td>5 (13.9 %)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0 (0 %)</td>
<td>3 (8.3 %)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>11 (40.7 %)</td>
<td>13 (36.1 %)</td>
<td></td>
</tr>
<tr>
<td>Arterial/capillary pH</td>
<td>7.18 (6.90–7.38)</td>
<td>7.16 (7.08–7.32)</td>
<td>0.434</td>
</tr>
<tr>
<td>Serum bicarbonate (HCO₃⁻), mmol/L</td>
<td>10.45</td>
<td>7.75</td>
<td>0.707</td>
</tr>
<tr>
<td>Sodium (Na), mmol/L</td>
<td>(3.65–19.00)</td>
<td>(4.00–18.00)</td>
<td></td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>2 (6.3 %)</td>
<td>0 (0 %)</td>
<td>0.211</td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>12.7 ± 5.85</td>
<td>9.75 ± 3.32</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Data presented as number and percentage, median and interquartile range, or mean ± standard deviation. A p-value less than 0.05 indicates statistical significance. T1D, type 1 diabetes; BMI, body mass index; SDS, standard deviation score; DKA, diabetic ketoacidosis; pH, positive potential of the hydrogen ions.

The proportion of T1D and T2D during pre-pandemic and pandemic periods

T1D accounted for 71.11 % of patients during the pre-pandemic period and 52.1 % during the pandemic. A significantly increased proportion of T2D was observed, rising from 28.89 % in the pre-pandemic to 47.89 % in the pandemic period, with a p-value of 0.042 (Figure 2).

Discussion

This study presents recent data on the incidence of childhood T1D and T2D, revealing a significant increase in the IR of both types of diabetes in Northern Thailand over a two-decade period. We have compiled the incidence of childhood T1D in Thailand over four decades, incorporating previous reports and the findings from this study (depicted in Figure 3) [4–10], illustrating the progressive increase in T1D incidence. Furthermore, we have demonstrated an increasing incidence of T2D during the pandemic period.

Figure 2: The proportion of T1D and T2D during the pre-pandemic and pandemic periods.

The rising incidence of T1D, as documented in our study, was consistent with findings from several studies in various countries [33–36]. However, it is important to note that while our results align with this trend, there are exceptions, such
as Sweden, where the incidence of childhood-onset T1D has plateaued [37], and Finland, where it has even decreased [38]. In Thailand, Rittipairoj T et al. recently reported a crude IR of T1D in children and young adults aged 0–19 years of 5.0/100,000 between 2015 and 2020. In this prior study, the diagnosis was reliant on diverse physicians entering ICD-10 codes and was recaptured with insulin prescriptions [39]. Consequently, there is a potential inclusion of T2D, neonatal diabetes, or monogenic diabetes requiring insulin in the reported incidence. In contrast, our study’s diagnosis was provided by pediatric endocrinologists, considering not only the clinical course but also conducting special investigations such as diabetes autoantibodies, c-peptide levels, etc. Therefore, we believe that our study accurately demonstrates the incidences of childhood T1D and T2D.

Additionally, our study sheds light on the growing incidence of childhood T2D in our country, a trend likely driven by the escalating issue of childhood obesity. According to the World Obesity Atlas, there is a projected high prevalence of childhood obesity, with an annual increase of 6.2 % during 2020–2035, resulting in an estimated 2.4 million obese children (aged 5–19 years) in Thailand by 2030 [40, 41]. Consequently, childhood T2D is emerging as a significant noncommunicable disease [32]. For context, Likitmaskul S. et al. previously reported an increase in the prevalence of childhood T2D from 5 % during 1986–1995 to 17.9 % during 1996–1999 [10]. Our study further highlights this concerning trend, revealing an increase in the prevalence of childhood T2D from 28.89 % during 2017–2019 to 47.89 % during 2020–2022. This finding was consistent with the results from previous studies. Schmitt JA. et al. reported a rise in new-onset T2D among youth in Alabama, USA during the COVID-19 pandemic with a monthly rate of 11.1 ± 3.8 prior to COVID-19 and 19.3 ± 7.8 during COVID-19 [42]. Marks BE. et al. demonstrated that incident cases of T2D increased by 182 % in Washington, District of Columbia, USA [43]. Along with the natural trajectory of T2D and the rise of childhood obesity, the increased incidence of childhood T2D during the pandemic, as observed in our study and other studies, might have been exacerbated by the national lockdown, leading to reduced physical activity and adverse health outcomes. Moreover, in our study, T2D cases had significantly higher random plasma glucose levels during the pandemic period. This finding may be associated with an emerging trend of increased insulin resistance during COVID-19 restriction measures [44].

Furthermore, our study demonstrated that the incidence of T1D was not different between the pre-pandemic and pandemic periods. This finding aligned with recent data from the worldwide SWEET registry, which analyzed information from 17,280 cases of T1D diagnosed between 2018 and 2021 from 92 centers worldwide, revealing no significant increase in new-onset childhood T1D during the COVID-19 pandemic [45].

Interestingly, our study found no increase in the prevalence of DKA, including its severity during the pandemic (66.6 % in the pre-pandemic vs. 58.3 % in the pandemic period). This contrasts with a recent meta-analysis indicating a 44 % higher risk of DKA during the COVID-19 period than in the pre-COVID-19 period [46]. This variation may be explained by the relatively high proportion of DKA in newly diagnosed young-onset diabetes (67.8 %) in our country before the COVID-19 era [27, 47]. Previous research has linked a lower DKA rate at presentation with a higher latitude and a higher Human Development Index (HDI) [48]. In Thailand, the high DKA rate at first presentation might be
attributed to its HDI of 0.777 (United Nations Human Development Report 2020) [47, 49]. Additionally, Thailand has a lower prevalence of T1D, leading to a lower level of awareness regarding T1D symptoms in children and adolescents, as well as limited familiarity with diabetes symptoms among parents and patients, and potentially even healthcare professionals [27, 47].

In the context of T1D, our study found that the length of hospital stay was shorter during the pandemic compared to the pre-pandemic period. This can be attributed to the fact that most hospitals were designated as referral centers, with beds primarily reserved for COVID-19 patients during the pandemic [50].

This study possesses several strengths. Firstly, it has completely captured all incident cases across all hospital levels and schools in our area. Secondly, the diagnosis of diabetes types was conducted by experienced pediatric endocrinologists using clinical assessments. The diagnosis was based on the initial presentation, clinical course, insulin dependency during the follow-up period, and additional investigations involving pancreatic autoantibodies and c-peptide levels. This meticulous approach ensures the accuracy of our reported incident rates.

It is essential to acknowledge the limitations of our study. Our research was exclusively conducted in the northern region of Thailand, potentially limiting the generalizability of our findings to other parts of the country. Nevertheless, our study has significantly contributed to illuminating the current incidence of childhood diabetes in Thailand. It is important to note that given the observational design of this study, it does not establish the causal effect of COVID-19 on the development of new-onset diabetes. Lastly, this study did not investigate the relationship between covid vaccination and the incidence of new-onset diabetes.

In conclusion, we demonstrate an increased incidence of childhood T1D and T2D in Northern Thailand over a two-decade period. The incidence of T1D and the prevalence of DKA, including its severity at onset, were not different between the pre-pandemic and COVID-19 pandemic periods. However, there was a notable increase in the incidence of T2D during the pandemic period. Our study may contribute to raising awareness among the public and healthcare personnel for early diagnosis of both types of diabetes in children and adolescents and the prevention of severe ketoacidosis. In particular, children and adolescents at risk for T2D should be screened and closely followed for early detection and management of T2D.

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Research ethics: This study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University (Research ID: PED-2565-08836) and by the Institutional Review Board of each participating center.

Informed consent: This study was granted an exemption from requiring written informed consent since this research involved no more than minimal risk to the participants.

Author contributions: PS, KW, and PD conceptualized and designed the study. All authors agreed with the conceptual framework of this study. PS, HT, and NS collected data. All authors provided clinical details. PS prepared the first draft of the manuscript. PS and PD performed the statistical analysis. PD and KW contributed to the review and editing of the manuscript. All authors have read and approved the final version of the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: All authors declare no competing interests.

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Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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