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RESEARCH ARTICLE

Evaluation and management of neonatal onset hyperinsulinemic hypoglycemia: a single neonatal center experience

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ABSTRACT

Objectives: To evaluate the clinical characteristics and treatment options of neonates requiring prolonged hospitalization due to persistent hyperinsulinemic hypoglycemia (HH).

Methods: This retrospective cohort study included infants >34 weeks of gestation at birth who were born in our hospital between 2018 and 2021, diagnosed with HH, and required diazoxide within the first 28 days of life. The baseline clinical characteristics, age at the time of diagnosis and treatment options in diazoxide resistance cases were recorded. Genetic mutation analysis, if performed, was also included.

Results: A total of 32 infants diagnosed with neonatal HH were followed up. Among the cohort, 25 infants were classified as having transient form of HH and seven infants were classified as having congenital hyperinsulinemic hypoglycemia (CHI). Thirty-one percent of the infants had no risk factors. The median birth weight was significantly higher in the CHI group, whereas no differences were found in other baseline characteristics. Patients diagnosed with CHI required higher glucose infusion rate, higher doses, and longer duration of diazoxide treatment than those in the transient HH group. Eight patients were resistant to diazoxide, and six of them required treatment with octreotide and finally sirolimus. Sirolimus prevented the need of pancreatectomy in five of six patients without causing major side effects. Homozygous mutations in the *ABCC8* gene were found in four patients with CHI.

Conclusions: The risk of persistent neonatal hyperinsulinism should be considered in hypoglycemic neonates particularly located in regions with high rates of consanguinity. Our study demonstrated sirolimus as an effective treatment option in avoiding pancreatectomy in severe cases.

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Hyperinsulinemic hypoglycemia; sirolimus; diazoxide; *ABCC8* mutation; neonate

Introduction

Hyperinsulinemic hypoglycemia (HH) is the leading cause of prolonged and persistent hypoketotic hypoglycemia in neonates. It arises from defective β-cell function in the pancreas, leading to uncoupling of insulin secretion from glucose metabolism [1]. Consequently, insulin secretion occurs excessively and uncontrollably, even in the presence of low plasma glucose concentrations in the affected neonates [2].

Hypoglycemia can present on a wide spectrum, from asymptomatic to life-threatening apnea or status epilepticus [3]. Due to the crucial role of glucose as the primary source of energy for the neonatal brain and the absence of ketone bodies as an alternative energy source in HH, persistent and severe hypoglycemia can result in irreversible cerebral damage and long-term neurological sequelae, including developmental delay, cerebral palsy, and epilepsy in infants [4,5]. Therefore, early recognition and prompt treatment are crucial.

Neonatal-onset HH encompasses both transient and congenital forms. Transient hyperinsulinism (THI) in neonates is a result of various risk factors such as perinatal asphyxia, intrauterine growth restriction (IUGR), fetal distress, small for gestational age (SGA), large for gestational age (LGA), and maternal diabetes mellitus [6]. Although there is no definitive definition of the duration of THI, it is often prolonged enough to necessitate treatment but resolves spontaneously within the first few months of life. In contrast,

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congenital forms of HH are typically resistant to treatment and are associated with mutations in the key genes responsible for insulin secretion regulation [7]. In the general population, the incidence of congenital hyperinsulinemic hypoglycemia (CHI) is estimated to be approximately one in 28,000–50,000 births, although it can reach to as high as one in 2700 births in countries with high rates of consanguinity [8,9].

The objective of this study was to evaluate the clinical characteristics and initial management strategies of patients diagnosed with neonatal-onset HH in a single, large neonatal center located in a region with a high rate of consanguinity.

Methods

This retrospective cohort study was conducted between January 2018 and March 2021 in a single tertiary-level neonatal intensive care unit (NICU) at the Gazi Yaşargil Training and Research Hospital in Diyarbakır, Turkey. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of our hospital (122/24.06.22).

Infants >34 weeks of gestation at birth who were born in our hospital and presented with hypoglycemia in the first 28 days of life were eligible if they met the following criteria:

1. Diagnosed with prolonged or recurrent hypoglycemia with inappropriately elevated or measurable insulin concentration at the time of documented hypoglycemia with low ketone bodies.
2. Required glucose infusion of >8 mg/kg/min.
3. Received diazoxide treatment.

Due to the discrepancies between the American Academy of Pediatrics (AAP) and Pediatric Endocrine Society (PES) recommendations regarding critical glucose thresholds in the first 48 h of life, at the time of initial hypoglycemia diagnose we opted for the PES definition of hypoglycemia as a glucose level ≤50 mg/dL (2.8 mmol/L) in the first 48 h of life and ≤60 mg/dL (3.3 mmol/L) thereafter [10,11]. The bedside glucose reagent test strips were used to screen hypoglycemia in babies at risk. For infants without clinical signs, laboratory blood glucose levels were measured to confirm the initial screening results. If infant had been fed within the first hour after birth, blood glucose levels were measured 30 min after the first feeding. If the glucose values were within the normal range, subsequent blood glucose measurements were taken every 3 h before the next feeding. Screening was terminated if no hypoglycemia was observed during 12 h screening time for infants who are at risk (LGA, infant of diabetic mother, or born due to fetal distress). In the cases of SGA and late preterm babies, the glucose screening process was continued for 24 h [12]. Hyperinsulinism was defined as elevated or measurable insulin level at the time of hypoglycemia in infants receiving glucose infusion rate (GIR) of >8 mg/kg/min [13].

Capillary blood ketone levels were evaluated at the patient's bedside using β-ketone strips (Optium-meter, Optium™ Xceed™/Abbott, Chicago, IL). A measurement of less than 0.6 mmol/L was considered negative for the presence of ketones. Free fatty acid levels were not used as criteria in our study because they were not available for measurement at our hospital. Infants with congenital or chromosomal anomalies and who had hypoglycemia due to causes other than HH were excluded. Furthermore, infants diagnosed with severe perinatal asphyxia, and those for whom complete data were not available were also excluded from the study.

Baseline clinical characteristics including gestational age, gender, birth weight, mode of delivery, and perinatal risk factors were obtained from the medical records. In addition, the initial laboratory features at the time of diagnosis, postnatal day at the diagnosis of HH, treatment options for patients during hospitalization, frequency of hypoglycemic episodes, and length of hospital stay were also recorded.

As per our unit policy, diazoxide was administered as first-line therapy if a patient had recurrent episodes of hypoglycemia despite receiving both enteral nutrition and intravenous glucose infusion of >8 mg/kg/min for more than 24 h. In line with PES recommendations, we used the target glucose threshold of >70 mg/dL for treatment in neonates diagnosed with HH [11]. We initiated treatment with diazoxide at a starting dose of 5 mg/kg/day, divided into three doses. While a definitive and widely accepted definition of diazoxide responsiveness is currently lacking, we define diazoxide unresponsiveness as the recurrent occurrence of hypoglycemia despite treatment with the maximum recommended dose of diazoxide in addition to enteral feeding and intravenous glucose infusion for ≥5 days. The maximum diazoxide dose was 15 mg/kg/d. The diazoxide response was defined as the ability to maintain normoglycemia following at least six hours fasting. Octreotide was used as the first-choice alternative treatment in diazoxide-unresponsive patients with a maximum dose of 30 μg/kg/d. In cases where patients

continued to experience recurrent hypoglycemic episodes despite receiving the maximum dose of octreotide, sirolimus was administered. These cases involved patients who had received maximum tolerable enteral nutrition at intervals not exceeding 2 h and intravenous glucose infusion for ≥5 days after octreotide administration. We started sirolimus treatment with a dose of 0.5 mg/m^2/day targeting plasma concentrations of 5–15 ng/mL. Sirolimus levels were closely monitored, and the dosage was adjusted to achieve target plasma concentrations. To minimize adverse effects of sirolimus, octreotide was restarted in patients when plasma sirolimus concentrations dropped below 5 ng/mL, and the patient remained normoglycemic. If the patient continued to maintain normoglycemia, sirolimus treatment was ultimately ceased. Patients remained on octreotide treatment, and octreotide was changed to long-acting release (LAR) form when patients reached 12 months of age.

We classified infants who responded to diazoxide and intravenous glucose infusion treatment and/or achieved remission solely through enteral feeding after cessation of treatment within the first four months as having THI. Infants with more severe symptoms requiring alternative treatments to diazoxide for prolonged periods, longer treatment beyond four months, and surgical intervention were classified as having CHI. As suggested by recent studies, genetic testing was performed only for patients who did not respond to diazoxide and/or whose medication was not successfully discontinued within the first four months [14]. Genomic DNA was isolated from the peripheral leukocytes using standard procedures. Subsequently, the coding exons and flanking intronic regions of the *KCNJ11* gene (NM_000525.3) and all coding regions and exon/intron boundaries of the *ABCC8* gene (NM_001287174.1) were analyzed by Sanger sequencing in both patients and their respective parents. In selected patients, comprehensive next-generation sequencing testing, including the detection of deletions and duplications, was performed.

Data were analyzed using SPSS version 24.0 for Windows (SPSS Inc., Chicago, IL). The normality of the data was first tested using the one-sample Kolmogorov–Smirnov test. Categorical variables were expressed as percentages and compared using Pearson's Chi-squared and Fisher's exact tests. Continuous variables were described as medians (minimum–maximum) and analyzed using the Mann–Whitney *U*-test when the data were not normally distributed.

Results

Of the 2920 infants admitted to the NICU during the study period, 1.1% were diagnosed with HH. A total of 32 infants that met the inclusion criteria were reviewed. The demographic characteristics of the infants are summarized in Table 1. The median gestational age and birth weight of the study group were 37 (34–40) weeks and 2825 (1800–5150) g, respectively. Twenty-two patients (68.8%) were at risk of hypoglycemia at birth, with at least one of the following conditions: SGA, LGA, late preterm, infants of diabetic mothers, and fetal distress. During the study, 25 infants were classified as having THI, and seven infants were classified as having CHI. The median birth weight was significantly higher in the CHI group, whereas no differences were found in other baseline characteristics. The critical sample levels, including insulin levels at diagnosis, were statistically similar between the groups. Ten patients were asymptomatic at the time of the first hypoglycemia episode and were diagnosed with routine screening due to increased risk. The consanguinity rate was high (37.5%); however, it did not significantly differ between the groups.

All infants included in the study required a glucose infusion of >8 mg/kg/min with a median of 10 (8–14.4). Particularly, the CHI group required a significantly higher GIR during their treatment course. Moreover, remission of hypoglycemic episodes took significantly longer in the CHI group. The median age at which diazoxide was started was 7 (3–24) days, showing no difference between the two groups. However, CHI patients required statistically higher maximum dose and longer duration of diazoxide. Although severe adverse effects such as respiratory decompensation and pulmonary hypertension were not observed in any patient, hypertrichosis was found in two patients, and fluid retention was reported in five patients. Thiazide diuretics were administered in cases of fluid retention. CHI cases demonstrated higher incidence of adverse effects of diazoxide. Additionally, eight infants were admitted to the NICU for reasons other than hypoglycemia, but hyperinsulinism was the primary cause of prolonged hospitalization in all patients. The length of hospital admission was higher in the CHI group. Feeding problems (sucking, swallowing, and vomiting) occurred in 37.5% of the patients and did not differ significantly between the groups. The majority of the affected infants received anti-reflux treatment and were fed via an orogastric tube (Table 2).

Eight infants (25%) were unresponsive to diazoxide therapy and required treatment with octreotide.

Table 1. Maternal and infant characteristics of hyperinsulinemic hypoglycemia patients.

	Total cohort, $n = 32$	THI, $n = 25$	CHI, $n = 7$	p Value[a]
Maternal age at birth, years[b]	28 (18–40)	29.5(19–40)	25 (18–38)	.16
Gestational age (weeks)[b]	37(34–40)	37 (34–40)	38 (34–40)	.28
Gender (male), *n* (%)	22 (68.8)	17 (68)	5 (71.4)	.52
Birth weight (g)[b]	2825(1800–5150)	2685(1800–5150)	3675(3160–4600)	***.03***
Cesarean section, *n* (%)	12 (37.5)	9 (36)	3 (42.8)	.37
Consanguinity, *n* (%)	12 (37.5)	8 (32)	4 (57.1)	.15
Late preterm, *n* (%)	5 (15.6)	4 (16)	1 (14.2)	.72
LGA, *n* (%)	9 (28.1)	6 (24)	3 (42.8)	.08
SGA, *n* (%)	6 (18.8)	6 (24)	–	.16
Gestational maternal diabetes, *n* (%)	5 (15.6)	4 (16)	1 (14.2)	.40
Fetal distress, *n* (%)	9 (28.1)	6 (24)	3 (42.8)	.32
Age at presentation, days[b]	2 (1–24)	2 (1–10)	2.5 (1–24)	.35
Presentation of hypoglycemia in the first 24 h of life, *n* (%)	18 (56.3)	14 (56)	4 (57.1)	.58
Critical sample profile[b]				
Glucose, mg/dL	23 (5–45)	24.9 (5–45)	19.5 (6–39)	.19
Insulin, mIU/L	28.1 (2.27–300)	26.8 (2.27–300)	29.2 (6.3–65)	.71
Cortisol, μg/dL	6.8 (0.6–24.8)	7.41 (0.6–24.8)	5.02 (1.22–12.7)	.28
Growth hormone, μg/L	23 (6–50)	23.7 (6–48)	24.5 (8–50)	.68
Serum ketones, mmol/L	0.3 (0.1–0.6)	0.3 (0.3–0.6)	0.3 (0.1–0.6)	.75

THI: transient hyperinsulinemic hypoglycemia; CHI: congenital hyperinsulinemic hypoglycemia; LGA: large for gestational age; SGA: small for gestational age.
ap Values $< .05$ were considered as significant. Significant p values are highlighted.
[b]Median (minimum–maximum).

Table 2. Comparison of hospital course of hyperinsulinemic hypoglycemia patients.

	Total cohort, $n = 32$	THI, $n = 25$	CHI, $n = 7$	p Value[a]
Maximum GIR, mg/kg/min[b]	10 (8–14.4)	10 (8–14.4)	12.5 (11–14)	***.03***
Administration of glucagon, *n* (%)	8 (25)	4 (16)	4 (57.1)	***.02***
Enteral feeding problems, *n* (%)	12 (37.5)	9 (36)	3 (42.8)	.58
Age at remission of hypoglycemia episodes, days[b]	13.5 (7–38)	12 (7–21)	25 (22–38)	***<.01***
Diazoxide				
Postnatal day of initiation, days[b]	7 (3–24)	7.5 (3–20)	7 (3–24)	.61
Maximum dose, mg/kg/d[b]	12 (8–15)	11.5 (8–15)	15 (15–15)	***<.01***
Adverse reaction, *n* (%)	7 (21.9)	3(12)	4 (57.1)	***.04***
Duration, days[b]	17.5 (9–32)	16.5 (9–32)	23 (17–32)	***<.01***
Length of hospital admission, days[b]	24 (14–124)	21 (14–32)	42.5 (39–124)	***<.01***

THI: transient hyperinsulinemic hypoglycemia; CHI: congenital hyperinsulinemic hypoglycemia; GIR: glucose infusion rate.
[a]p Values $< .05$ were considered as significant. Significant p values are highlighted.
[b]Median (minimum–maximum).

Table 3. Treatment course of congenital hyperinsulinemic hypoglycemia group during hospitalization.

	CHI, $n = 7$
Octreotide, *n* (%)	7 (100)
Postnatal day of initiation, days[a]	16 (11–30)
Maximum dose, mg/kg/d[a]	22.5 (18–25)
Duration, daysa,b	20 (14–36)
Sirolimus, *n* (%)	6 (85.7)
Postnatal day of initiation, days[a]	22 (18–34)
Adverse reaction, *n* (%)	2 (33.3)
Duration, days[a]	82 (32–98)
Need of surgery, *n* (%)	1 (14.2)

[a]Median (minimum–maximum).
[b]Duration of drug treatment during hospitalization.

Furthermore, six of these patients (18.8%) did not respond to octreotide and required sirolimus. One patient developed sepsis, and one patient had mild elevations in liver enzymes and hyperglycemia during treatment with sirolimus, which prompted dose reduction. However, only one patient underwent subtotal pancreatectomy (Table 3). Hypoglycemia resolved in after achieving minimum target concentration of 5 ng/mL in all patients during the study period except these case.

During their NICU stay, seven diazoxide-unresponsive patients who needed prolonged treatment underwent genetic testing, with four of them found to have pathogenic mutations in the *ABCC8* gene (Table 4).

Discussion

In the present study, during the 3-year study period, a total of 32 infants diagnosed with neonatal-onset HH were followed, with 25 infants classified as THI and seven classified as CHI. Among the patients, eight were resistant to diazoxide, and six of these patients required sirolimus treatment. Of seven patients who

Table 4. Characteristics of congenital hyperinsulinemic hypoglycemia patients.

	Age at diagnosis	Gestational age (weeks)	Gender	Birth weight (g)	Weight[a] for age	Gene	Duration of hospital stay (days)
1[b]	Day 1	34	M	3160	LGA	*ABCC8*, homozygous, c.4212_4214del, p.Ile1405del	42
2[c]	Day 1	40	M	3700	AGA	–	124
3	Day 3	37	M	3800	LGA	–	39
4	Day 8	38	M	4600	LGA	*ABCC8*, homozygous, c.3554C > A, p.Ala1185Glu	43
5	Day 24	38	F	3600	AGA	*ABCC8*, homozygous, c.176A > C, p.His59Pro	40
6	Day 4	40	F	3650	AGA	*ABCC8*, homozygous, c.3512delT, p.Leu1171fs	64
7	Day 1	38	M	3550	AGA	–	42

[a]LGA: large for gestational age; AGA: appropriate for gestational age.
[b]Sirolimus was restarted after a one-year cessation period due to the recurrence of hypoglycemia.
[c]These case underwent partial pancreatectomy. The patient had low scores in Bayley II Mental Developmental Index at 24 months, and treated for refractory epilepsy.

underwent genetic testing, four were identified as having a homozygous *ABCC8* mutation.

There is a discrepancy in the management of neonatal hypoglycemia during the initial 48 h of life between neonatologists and pediatric endocrinologists. The AAP considers low glucose levels, as low as 20–25 mg/dL in the first hour, as part of the normal adaptation for postnatal life and suggests using lower glucose value ranges during this period [3,10]. In our cohort, 10 patients (31.3%) who were asymptomatic and diagnosed through routine screening due to an increased risk had lower glucose levels than PES recommendations. Initially, our approach involved monitoring the infants by encouraging breastfeeding and avoiding separation from the mother. However, due to recurrent hypoglycemic episodes, admission to the NICU was required for further treatment. Our findings showed that, although it is important to avoid administering excessive treatment to asymptomatic neonates undergoing routine postnatal adaptation, the risk of persistent neonatal hyperinsulinism should not be forgotten.

Despite the known risk factors for neonatal hyperinsulinism, such as SGA, LGA, late preterm, having a diabetic mother, and experiencing fetal distress, 31.2% of the infants did not possess any risk factors. Furthermore, there was no significant difference in the incidence of risk factors between the two groups. Considering that the CHI group had a significantly higher birth weight in our study, it is possible that a higher birth weight in the absence of additional risk factors could serve as a predictor for CHI. Although the incidence of initial hypoglycemic episodes within the first 24 h did not show a significant difference between the groups, our study revealed a higher occurrence of first hypoglycemic episodes after 24 h in both at-risk group and the group without known risk factors compared to previous studies [15]. Therefore, we altered our protocol for monitoring neonates by implementing a policy of prolonged screening for those who are at risk.

Diazoxide is the first-line treatment for prolonged hyperinsulinism, with a reported efficacy range of 41.2–81.8% in previous studies [16,17]. Diazoxide is generally effective in children with complete K_{ATP} channels and previous studies showed that the majority of unresponsive patients are likely to have mutations in the *ABCC8* or *KCNJ11* genes [18,19]. In this cohort, consistent with the literature, 75% of patients responded to diazoxide [17]. Interestingly, although severe side effects such as cardiotoxicity, respiratory decompensation, and pulmonary hypertension have been reported in up to 7% of patients treated with diazoxide, we did not observe any severe adverse effects in either group [20,21]. This difference could potentially be attributed to the exclusion of infants <34 weeks gestation and the comparatively shorter median duration of diazoxide treatment in the present study. Given that the patient characteristics were comparable between groups, the increased occurrence of side effects observed in the CHI group, which received higher doses for a longer duration, can also be attributed to the dose-dependent effect. In our study, although the timing of diazoxide treatment remains debatable, early initiation of diazoxide compared to previous studies resulted in a shorter median duration of hospital stay [22]. A study conducted in the UK showed that, despite its rarity, the expenses associated with caring for infants with HH can be a significant burden [23]. In addition to inpatient medical care

costs, we believe that shorter hospital stays can lead to earlier mother-child bonding.

In diazoxide-unresponsive infants, we used the somatostatin analogue, octreotide. Of interest, although the efficacy of octreotide in the treatment of HH has been long recognized, 75% of the infants in our cohort did not respond to octreotide. In the unresponsive cases, sirolimus was administered. Sirolimus inhibits the mTOR pathway, which has been implicated in the regulation of beta-cell mass, proliferation, and size, potentially limiting the production of insulin from beta cells [24]. In our cohort of six patients treated with sirolimus, only one patient required subtotal pancreatectomy. Our findings indicated that sirolimus resulted in a higher rate of success in avoiding pancreatectomy in the short term compared to previous studies [25]. However, case series have reported rate of complications, including immunosuppression, abnormalities in renal function, and episodes of transient elevation of aminotransferase levels as high as 86.4% in patients treated with sirolimus [24]. Furthermore, our center had unfavorable experience with adverse effect of sirolimus before and reported the first cases of sirolimus-induced hepatitis in CHI [26]. Among the six patients in the study who received sirolimus, one developed hyperglycemia and mild elevations of liver enzymes that required dose reduction. Another infant developed sepsis during hospitalization, resulting in the temporary cessation of the drug. This patient had additional risk factors including the presence of a central catheter, early antibiotic use, prolonged hospitalization, and sepsis developed at an early stage of drug administration. These factors suggest that sepsis may be attributed to causes other than sirolimus alone. It is worth noting that the primary complications associated with sirolimus were reported with prolonged drug use; thus, caution must be exercised when using this drug. In our study, administration of sirolimus was limited to a maximum of 3.5 months, after which the patients were maintained on conventional therapy and remained normoglycemic. The CHI patients restarted octreotide treatment in the process of cessation of sirolimus and octreotide. LAR was started after 12 months in the majority of these patients.

According to an algorithm, genetic testing is recommended only for patients who are diazoxide unresponsive, need high diazoxide dose for prolonged periods of time, or in patients who continue on medication after 6 months [27]. A comprehensive study conducted in Finland focusing on the genetic characterization of persistent HH cases did not identify any carriers of pathogenic variants among patients with THI [7]. Based on these findings, genetic testing was performed solely for patients diagnosed with CHI in our study. We identified genetic mutations in four of the seven infants who underwent early genetic testing due to resistant hypoglycemia. All patients had homozygous mutations in *ABCC8* gene, which is consistent with a large study that showed mutations in *ABCC8* and *KCNJ11* gene as the most common causes of CHI in Turkish patients [28]. All mutations were previously reported in the literature [26,28,29]. Genetic analysis in all cases demonstrated both parents to be carriers of heterozygous pathogenic variant of the *ABCC8* gene, indicating biparental inheritance. In majority of HH patients, the identified genetic cause is a single-gene defect affecting pancreatic β-cells and their insulin secretion regulation pathway [2]. There are typically no other main organ manifestations apart from the abnormality in metabolic and endocrine functions. However, both transient and congenital forms of HH can also be observed in a variety of syndromic disorders (e.g. Beckwith-Wiedemann syndrome, Kabuki syndrome, CHARGE syndrome) [30,31]. Nonetheless, none of the patients in our cohort exhibited any syndromic features.

Our study has several limitations. First, we primarily focused on the identification and management of these patients during their hospitalization in the NICU and did not report the long-term morbidities associated with HH. Second, we focused solely on the analysis of the two most prevalent genes in CHI and next-generation sequencing testing was performed in selected patients. Lastly, we did not report the adverse effects of drugs during long-term administration.

In conclusion, our study provides a perspective on the diagnosis of persistent HH and emphasizes the differences in the clinical characteristics and management strategies between THI and CHI. The higher rate of sirolimus use in patients with CHI coupled with its effectiveness in avoiding pancreatectomy, may contribute to the development of an optimal treatment approach for CHI.

Author contributions

HB and NO were primarily responsible for protocol development and the analytic framework of the study, outcome assessment, and manuscript preparation. HB, KC, and FFT had primary responsibility for reviewing the files, patient screening, enrollment, and data entry, and prepared the manuscript with NO. MNO contributed to preparation and revision of the manuscript.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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