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Hepatic Steatosis in Infancy: The Beginning of Pediatric Nonalcoholic Fatty Liver Disease?

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Objectives: Nonalcoholic fatty liver disease is clinically silent and the age of its onset is unknown. Fatty liver can occur as early as in utero in the context of an unfavorable maternal metabolic environment. Our objective was to determine the prevalence of hepatic steatosis in a cohort of previously healthy infants less than 3 months of age.

Methods: Retrospective study of all abdominal computed tomography (CT) scans performed from 2009 to 2019 for the investigation of trauma. Two independent reviewers applied published criteria to determine the presence of hepatic steatosis. Descriptive statistics were used. The groups with and without steatosis were compared using Wilcoxon-Mann Whitney or Fisher exact test.

Results: Of 119 CT scans available in infants younger than 3 months of age, 65 were performed in previously healthy infants for the investigation of trauma. The included population was predominantly male, non-Hispanic, with a median age of 60 days (interquartile range, 34–73 d). Depending on the criteria used, 23% or 26% of infants had evidence of fatty liver. The prevalence of maternal obesity and/or diabetes was 11% (of the 65 pregnancies) but there was no significant difference in maternal risk factors between infants with and without evidence of steatosis.

Conclusions: Findings suggest CT evidence of hepatic steatosis in up to a quarter of otherwise healthy infants ≤3 months of age. This may represent early manifestation of pediatric nonalcoholic fatty liver disease. The natural history and pathophysiology of this condition need to be studied to determine optimal detection, prevention and early intervention strategies.

Key Words: liver steatosis, nonalcoholic fatty liver disease, pediatric obesity, x-ray computed tomography

What Is Known

- The prevalence of nonalcoholic fatty liver disease (NAFLD) has increased with rising obesity in the pediatric population.
- NAFLD is currently the most common chronic liver disease in children.
- Because NAFLD is a clinically silent disease, the age of its onset is not known.

What Is New

- Computed tomography evidence of hepatic steatosis is present in approximately a quarter of otherwise healthy infants 3 months of age or younger.
- Pediatric NAFLD may present as early as 3 months of age.

Translation Impact

- Incidental findings of hepatic steatosis on imaging should be followed.
- Studies should be performed to discover prevention strategies in young children.

INTRODUCTION

The prevalence of nonalcoholic fatty liver disease (NAFLD) has increased with rising obesity in the pediatric population, and NAFLD is currently the most common chronic liver disease in children (1–5). Because NAFLD is a clinically silent disease, the age of its onset is not known. However, emerging evidence describes it occurring with alarming prevalence even in preschool age children (6). Notably, a younger age of presentation has been associated with a more severe disease phenotype (7). This is concerning, as NAFLD is the currently the fastest rising indication for liver transplantation in young adults in the United States (8). Thus, the onset and natural history of pediatric NAFLD warrant further elucidation to help refine screening recommendations and guide prevention strategies, with the ultimate goal of halting disease development and progression.

Hepatic steatosis has been reported to occur as early as in utero. Fetal hepatic steatosis was detectable in an autopsy study in 42% of 81 stillborns and was significantly more common in the stillborns of mothers with diabetes (9). Furthermore, a limited number of studies have investigated the presence of hepatic steatosis in neonates. Using magnetic resonance imaging, Modi et al (10) showed that maternal body mass index was predictive of intrahepatocellular lipid content at a mean age of 12 days. Similar results were shown in a smaller study by Brumbaugh et al (11). Beyond these observational

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The authors report no conflicts of interest.

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studies, emerging translational data have provided initial insights into the pathogenesis of this condition (12–15).

Despite such key advances in the field, the natural history of the liver disease detected in utero and during the neonatal life is not defined. It is not yet clear whether the hepatic steatosis that develops as a result of an unfavorable maternal metabolic environment resolves, or whether it persists, only to be diagnosed later in childhood. More importantly, in spite of the growing number of studies suggesting that the prevalence of NAFLD among the very young is significant (6, 16), clinical practice is still focused on only screening children at risk for NAFLD starting at 9–11 years of age, and rarely sooner (1). The limitations of this approach are highlighted by the significant proportion of children a who already have advanced disease at the time of diagnosis (17).

The objective of our study was to determine the prevalence of imaging evidence of hepatic steatosis by computed tomography (CT) in a cohort of previously healthy infants between birth to 3 months of age.

METHODS

This was a retrospective study performed at Cincinnati Children's Hospital Medical Center (CCHMC). Patients were included if they had undergone an abdominal CT scan at CCHMC between November 1, 2009, and December 1, 2019. Additional inclusion criteria were age at the time of abdominal imaging of 3 months (corrected age) or younger. Subjects were excluded if their study was a noncontrast CT or was insufficient to determine the presence of hepatic steatosis (eg, due to liver injury or asplenia). Noncontrast CT examinations were excluded as these are very rarely performed in this age group and attenuation measurements derived from these examinations are not comparable to those derived from contrast-enhanced CT examinations. Preterm infants born before 28 weeks gestational age and those with a known diagnosis that could contribute to hepatic steatosis were excluded. For infants with multiple examinations, the first CT scan was selected for review. Institutional Review Board approval was obtained prior to the start of study activities (CCHMC IRB No. 2019-1294). Research electronic database capture was used for secure data collection (18).

Patient Identification

Eligible patients were identified through a query of Radiology Department records (Softek Illuminate).

Clinical Review

Electronic chart review was completed to collect the clinical, laboratory, and imaging variables of interest. Birth history and demographic data, as well as information from the time of imaging, such as anthropometric measurements, medications, and laboratory values obtained on the day of imaging, as well as indication for imaging, were collected. Birth measurements were classified per the Centers for Disease Control and Prevention growth charts for term infants and per the Fenton growth charts for preterm infants (19).

Imaging Review, Image Analysis, and Steatosis Classification

CT examinations had been performed with intravenous iodinated contrast material administered at 1–1.5 mL/kg. Images were routinely reconstructed at 3 mm axial intervals for patients in this age group.

Image measurements were performed by 2 independent observers who were blinded to one another's measurements.

Liver and spleen parenchymal attenuation were measured in Hounsfield units (HU) by placement of similar sized, approximately 100 mm^2, round regions of interest (ROIs) in the liver and spleen avoiding large vessels and lesions, if present. ROIs were placed on the same axial slice and, for the liver, 1 ROI was placed in each hepatic lobe (right and left) with liver attenuation calculated as the average of the 2 liver measurements (Fig. 1A). Smaller ROIs, to fit within the vessel confines, were placed in the main portal vein and abdominal aorta to measure vascular attenuation (Fig. 1B).

For the purpose of study reporting, the measurements made by 1 pediatric radiologist were utilized. Based on these measurements, hepatic steatosis was considered present according to the following published criteria:

- Portal venous phase postcontrast liver-spleen attenuation <–20 HU (hereafter called LS20 criteria) (20).
- Portal venous phase postcontrast: L–B < 101 HU, where L–B = (L–0.3 × [0.75 × P + 0.25 × A])/0.7 where L, P, and A represent the attenuation of the liver, main portal vein, and abdominal aorta, respectively (hereafter called LB101 criteria) (21).

Agreement between observers was calculated at both the HU level for liver and for spleen, and at the patient classification level (steatosis yes/no based on the criteria above).

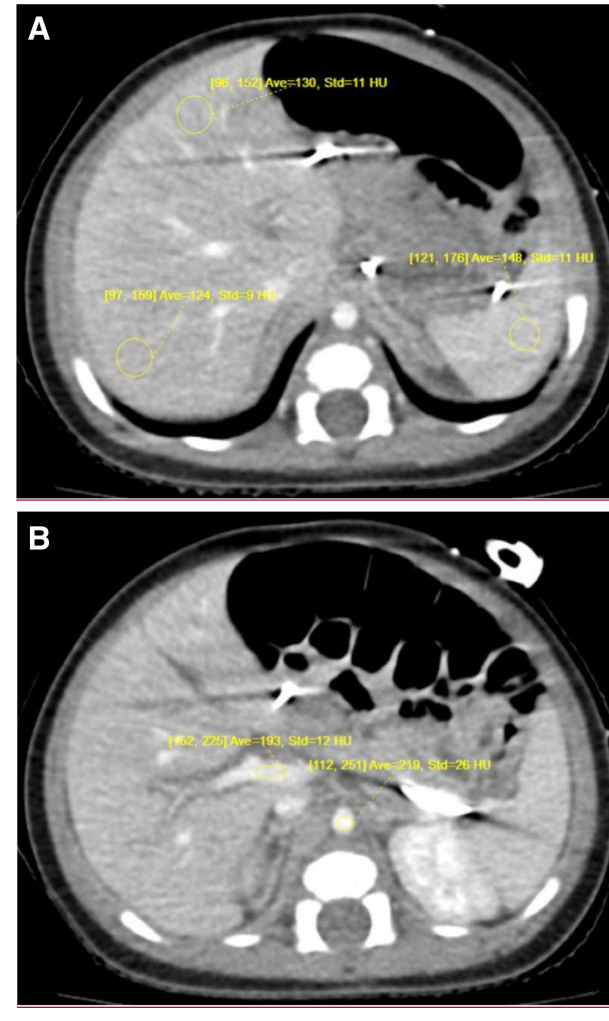

FIGURE 1. Example image measurement is shown. Similar sized regions of interest (yellow ovals) were measured on the same axial slice. Measurement of liver and spleen parenchymal attenuation (A) and main portal vein and abdominal aorta (B) on axial CT images obtained of a 2-mo-old Caucasian boy with hepatic steatosis. CT = computed tomography; HU = Hounsfield units.

Statistical Analyses

Descriptive statistics (proportions, means with SDs, medians with interquartile range [IQR]) were used to describe the study cohort. Independent student *t* test or Wilcoxon-Mann Whitney test were used to compare continuous variables depending on their distribution, while chi-square with Fisher exact test were used to compare categorical variables, between groups of infants with and without hepatic steatosis. Kappa statistics were used to evaluate the agreement of image measurements between 2 investigators with the 95% confidence interval (bias-corrected bootstrap interval). A 2-sided probability value of <0.05 was considered significant.

RESULTS

A total of 119 patients had undergone abdominal CT scans during the study period. Of those, 65 were previously healthy infants 3 months of age or younger (Fig. 2). The majority of these patients were term non-Hispanic males (Table 1). Their median age at the time of imaging was 60 days (IQR, 34–73 d). The indications for ordering the vast majority (59/65, 91%) of CTs were trauma, including nonaccidental trauma (NAT), fall, and motor vehicle accident. Thirty of the CTs were ordered for clinical suspicion of NAT. The remaining clinical and laboratory information is summarized in Table 1.

Using previously reported LS20 criteria to determine the presence of steatosis, 23% and 28% of the patients were found to have imaging findings suggestive of steatosis by the first (radiologist) and second investigators. Further, 26% and 28% of patients were found to have imaging findings consistent with steatosis using the LB101 criteria by the same 2 investigators. From here on, the remaining analyses are presented for steatosis determined using the LB101 criteria, as this approach provided the highest power to determine statistically significant differences between groups.

The distribution of imaging evidence of steatosis was not statistically different between ages, seen in 17% (n = 2/12) of those in the first 1 month life, 30% (n = 7/23) of those in the second month of life, and 27% (n = 8/30) of those in the third month of life ($P = 0.657$).

The frequency of maternal risk factors and the remaining infant clinical variables assessed were not significantly different between those with and without imaging evidence of hepatic steatosis (Table 2). Similarly, the rate of weight gain from birth to the time of imaging was not significantly different between those with and without imaging evidence of steatosis. Forty-one percent (7/17) of the infants with imaging evidence of steatosis had NAT.

Serum markers of liver injury were statistically significantly different between infants with and without imaging evidence of steatosis, with alanine aminotransferase (ALT) levels being lower in those with steatosis (median ALT 25 U/L [IQR 20–52 U/L] versus 75 U/L [IQR 37–123 U/L]; $P = 0.018$ and ALT distribution shown in Fig. 3). Similarly, serum aspartate aminotransferase levels were lower in those with steatosis (median aspartate aminotransferase 36 U/L [IQR 26–61 U/L] versus 72 U/L [50–146 U/L]; $P = 0.031$), while alkaline phosphatase levels were comparable between the groups (median alkaline phosphatase 205 U/L [IQR 169–260 U/L] versus 263 U/L [IQR 214–332 U/L]; $P = 0.098$). Random serum glucose levels were not different between those with and without evidence of hepatic steatosis (median glucose 87 mg/dL [IQR 79–109 mg/dL]

TABLE 1. Characteristics of the study cohort (n = 65)

Variable	Result
Sex, male, n (%)	47 (72)
Ethnicity, non-Hispanic, n (%)	63 (97)
Race, n (%)	
White	48 (74)
African American	15 (23)
Unknown	2 (3)
At birth	
Maternal age at delivery (y)	24 (22–30)
Maternal overweight, obesity, or diabetes (gestational, type 1 or 2), n (%)	7 (11)
Gestational age (wk)	39 (38–40)
Mode of delivery, n (%)	
Vaginal	23 (35)
C-section	13 (20)
Missing data	29 (45)
Birth weight status, n (%)	
Appropriate for gestational age	29 (45)
Small for gestational age	3 (5)
Large for gestational age	2 (3)
Missing data	31 (47)
Birth weight (g)	3470 (2971–3720)
Birth weight *z* score	0.156 (–0.577 to 0.545)
Birth length (cm)	50.9 (49.5–52.7)
Birth length *z* score	0.439 (–0.530 to 0.962)
Birth head circumference (cm)	34.4 (34.0–36.0)
At the time of abdominal imaging	
Age (d)	60 (34–73)
Weight (g)	4715 (4250–5500)
Length (cm)	53.0 (51.5–57.0)
ALT (U/L)	59 (26–112)
AST (U/L)	63 (35–131)
Alkaline phosphatase (U/L)	253 (194–304)
Glucose (mg/dL)	88 (81–108)

Continuous variables are expressed as medians (IQR). ALT = alanine aminotransferase; AST = aspartate aminotransferase; IQR = interquartile range.

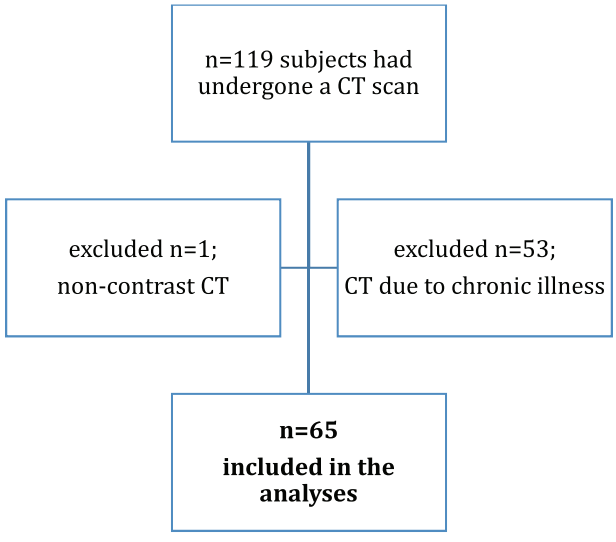

FIGURE 2. Flowchart demonstrating the selection of patients. CT = computed tomography.

TABLE 2. Comparison of subjects with and without imaging evidence of hepatic steatosis based on LB101 criteria

Variable	Steatosis, n = 17	No steatosis, n = 48	*P*
Gestational age (wk)	39 (±1)	38 (±3)	0.138
Birth weight (g)	3625 (±655)	3215 (±664)	0.124
Maternal overweight, obesity, or diabetes (gestational, type 1 or 2; %)	18	8	0.366
Sex, male %	71	73	1.000
Ethnicity, non-Hispanic %	100	96	1.000
Age at CT (d)	53 (±21)	55 (±24)	0.696
Weight at CT (g)	4911 (±756)	4931 (±1032)	0.934
Rate of weight gain since birth (g/d)	25 (±12)	28 (±20)	0.624

CT = computed tomography.

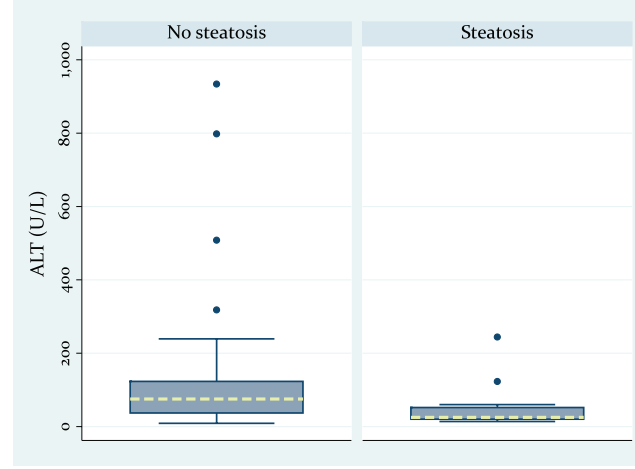

FIGURE 3. Box plots showing the distribution of serum ALT levels of infants with and without steatosis. The dashed lines represent the median ALT for each group ($P = 0.018$). ALT = alanine aminotransferase.

versus 89 mg/dL [IQR 81–108 mg/dL]; $P = 0.836$). Five infants had radiographic evidence of focal abdominal injury, but no infants meeting LB101 criteria for steatosis had radiographic evidence of abdominal injury.

The kappa coefficient between the 2 independent reviewers who made the imaging measurements on the available CT scans was 0.763 (95% confidence interval, 0.646–0.880). None of the clinically generated radiology reports for the CT scans had made note of the presence of steatosis.

DISCUSSION

In this study, we investigated the prevalence of imaging findings suggesting hepatic steatosis in previously healthy infants who had undergone abdominal CT imaging over the past decade at our institution. In our population, approximately 1 in 4 infants, at a median age of 2 months, had evidence of hepatic steatosis. This was in spite of a generally low prevalence of other risk factors, such as prematurity, maternal obesity/gestational diabetes, or rapid weight gain in the first weeks of life. Furthermore, steatosis was seen in the context of generally low, albeit borderline elevated (22), serum aminotransferase levels.

We chose to investigate hepatic steatosis in infants up to 3 months of age for several reasons. First, this age group still relies entirely on breast milk or formula for their nutrition. This eliminates the variation that dietary exposures from solids or other beverages introduce that can, in turn, have an impact on the risk of steatosis development (23, 24). Second, the first 3 months of life are a period of transition from the in utero environment to infancy. The only reports available to date on early onset hepatic steatosis are from the first weeks of life (<4 wk of age) and are likely most reflective of the impact of the maternal metabolic environment (10, 11). We felt that our cohort, being representative of the first 3 months of life, is reflective of the metabolic transition that occurs after birth. Third, young infants are less likely to have been exposed to other risk factors, such as antibiotics, which can alter their risk of developing hepatic steatosis (25). Lastly, studying the presence of steatosis in early infancy is relevant, as it is currently not known.

In clinical practice, particularly for screening purposes, clinicians need to be aware of the risk factors that predispose infants to hepatic steatosis. The literature to date has implicated maternal obesity and maternal diabetes in this process (9–11). In our study, maternal risk factors were not different between those with and without hepatic steatosis. When using the LB101 criteria to determine the prevalence of steatosis, we did note a potentially clinically, yet not statistically, significant difference in the prevalence of steatosis among infants exposed to maternal risk factors (43%) and that of infants not exposed to these risk factors (24%; $P = 0.366$). Given the low rates of maternal obesity and diabetes in our cohort, there may have been underreporting, so that we were not able to demonstrate the true impact of these risk factors on the risk of infantile steatosis. Alternatively, one can postulate that the metabolic effects of the unfavorable in utero environment on the infant are short-lived and no longer evident by 2 months of age (the median age of our cohort at the time of imaging). This could explain the discrepancy between our findings and those of previous investigators showing a greater prevalence of hepatic steatosis the first month of life in infants born to mothers with diabetes or obesity. The natural history of early onset fatty liver disease remains to be investigated in prospective, birth cohort studies.

Another finding that suggests that extrauterine factors potentially contributed to the development of hepatic steatosis in our cohort was differences in the prevalence of steatosis among infants of different age groups. Interestingly, the prevalence of steatosis was lowest among infants in the first month of life (17%), compared with those in the second and third month (30% and 27%, respectively; although not a statistically significant difference, $P = 0.657$). This may be in part reflective of the weight loss naturally seen in the first few days of life, which, if excessive, could mobilize available hepatic fat stores. Given the retrospective nature of the study, detailed dietary information was not available; however, rates of weight gain were similar between the groups, suggesting that at minimum caloric intake differences were unlikely. It is possible that genetic predisposition, intestinal microbiome differences and socioeconomic risk factors placed certain patients at increased risk of hepatic steatosis.

According to the North American pediatric guidelines, at risk individuals should be screened for NAFLD at 9–11 years of age (1). This recommendation was made in part due to the limited availability of data regarding the prevalence and progression of NAFLD at younger ages. Our study highlights that, not only is imaging evidence of hepatic steatosis prevalent in infancy, but that it is highly likely to be disregarded or underdiagnosed. The CT scans we reviewed showed evidence of hepatic steatosis in 23%–26% of patients; however, in clinical practice, this finding was not mentioned or investigated further in any patient. The lack of reporting on incidental findings of steatosis on imaging has been previously noted in the literature (26).

Furthermore, the median aminotransferase elevation in those with steatosis was mild (and lower than that of the nonsteatosis group, which potentially suggests extrahepatic tissue contribution to the aminotransferase elevation in the nonsteatosis group), as is typically the case with pediatric NAFLD (27–29). These 2 factors likely lead to underdiagnosis of NAFLD, particularly in age groups, such as that of infants, which are not thought to be high risk for hepatic steatosis. This is problematic due to the increasing identification of severe liver disease at a young age (7). It is possible that the origin of the liver disease of children who present with severe steatohepatitis and advanced fibrosis in early childhood is in infancy, raising the possibility that improved screening and intervention approaches could prevent liver disease progression. The latter remains to be investigated further.

Our study has several limitations. First, this was a retrospective study and for that reason some data of interest were missing. Maternal diagnoses were most likely underreported in the infant's medical record. Even when a birth record is available, the electronic medical record automatically populates the mother's problem list into the newborn documentation. Obstetricians may miss adding overweight status as a comorbidity into the mother's problem list. A study of pregnant mothers in Ohio revealed that 46.6% were overweight or obese prior to conception (30). This could have affected our ability to discern the association between maternal risk factors and infantile steatosis. Second, the methodology we used to assess the presence of hepatic steatosis was based on clinically acquired CT imaging rather than imaging targeted at identification and quantification of hepatic fat (eg, MRI). Further, while previously described and utilized in studies of NAFLD with good diagnostic performance, the CT criteria used to suggest the presence of steatosis were developed based on adult populations and have not been independently verified in the pediatric or neonatal populations (2, 6). Third, while we focused our analysis on a previously healthy patient population, it is possible that the cohort was biased relative to the general population, as 46% were undergoing a workup for NAT. This may have introduced educational, socioeconomic, or other biases. Known risk factors for NAT include prematurity, drug exposure, and public insurance. It is possible these are also risk factors for steatosis (31, 32). Fourth, trauma may have affected the serum aminotransferase levels and for that reason, it is challenging to comment further on the observed differences in the aminotransferase levels between those with and without steatosis. Patients possibly exposed to blunt abdominal trauma were not excluded from this study. Fifth, our cohort was predominantly composed of non-Hispanic patients and so the results may not be generalizable to other ethnicities. Finally, since these patients were not followed over time, it is unknown if they eventually received a diagnosis such as an inborn error of metabolism that could cause steatosis.

In summary, our findings are suggestive that there is CT evidence of hepatic steatosis in up to 1 in 4 predominantly non-Hispanic, male infants younger than 3 months of age. The pathophysiology and natural history of this early onset steatosis needs to be investigated further, to determine whether it is linked to the severe pediatric NAFLD phenotypes seen in early childhood. It is crucial to implement prevention strategies since treatment options for pediatric NAFLD are still lacking.

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M.M. conceptualized and designed the study, carried out the initial analyses, drafted the initial article, and reviewed and revised the article. She is the guarantor of the articles. A.T.T. and M.M. coordinated and supervised data collection, reviewed, and revised the article. K.M. and T.Y. assisted with data collection, carried out the initial analyses, drafted the initial article, and critically reviewed and revised the article for important intellectual content. C.G.A. assisted with data collection and revised the article for important intellectual content. S.D. and C.G. participated in the interpretation of the data, critically reviewed and revised the article for important intellectual content. All authors approved the final article as submitted and agree to be accountable for all aspects of the work.

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