Research Article

Selective lactase deficiency is common in pediatric patients undergoing upper endoscopy

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Abstract

Lactase deficiency can lead to significant symptoms in the pediatric population. To date, few studies have examined the prevalence of enzyme testing-based lactase and other disaccharidase deficiencies (DDs) in pediatric patients undergoing upper endoscopic evaluation. The primary objective of this study was to determine the prevalence of selective lactase and other DDs amongst a large cohort of pediatric patients with and without inflammatory bowel disease (IBD: Crohn's disease and ulcerative colitis) via a chart review of 739 patients who underwent esophago-gastro-dudenoscopy EGD between April 2010 and August 2016. We identified 560 pediatric patients (ages 1-18 years) who underwent mucosal enzyme testing at the time of their EGD. The overall rate of lactase deficiency (LD) was 39%. LD positively correlated with age (p=0.00017), but there was no significant difference between age matched IBD and non-IBD patients (45% vs. 42% p=0.68). Four patients (0.17%) were found to have selective maltase deficiency. No selective sucrase or palatinase deficiency was identified. Statistically significant differences occurred in lactase deficiency amongst patients of different races. In conclusion, lactase deficiency is a relatively common finding in children undergoing EGD though at no increased rate amongst the IBD patient population. Disaccharidase testing should be considered in pediatric patients undergoing EGD.

Introduction

Lactose is a disaccharide composed of galactose and glucose, most commonly found in mammalian milk and milk products. Lactase is the enzyme located on the brush border of duodenal and jejunal enterocytes that is responsible for the breakdown of this sugar. The majority of human infants are born with high levels of lactase, as congenital lactase deficiency is an extremely rare condition (Diekmann *et al.* 2015). In fact, rather than being born with a paucity of lactase, the majority of humans lose lactase activity with advancement of age. The symptoms of lactase deficiency can include abdominal pain, bloating, increased flatulence, and diarrhea, which are caused by the processing of undigested lactose by colonic bacteria (Heyman 2006). Although lactase deficiency is the most common disaccharidase deficiency (DD), there are several other disaccharidases, also located on the brush border of enterocytes including sucrase, maltase, and palatinase. These disaccharidases are important in the breakdown of dietary disaccharides.

Inflammatory bowel disease (IBD) is a family of chronic inflammatory intestinal disorders, including Crohn's disease (CD) and ulcerative colitis (UC) for which the etiology is largely unknown. The symptoms of IBD flares can be similar to that of lactose malabsorption: abdominal pain, diarrhea, bloating. To date, there have been few studies examining the frequency of lactase deficiency amongst the pediatric IBD population; even fewer have looked at that of sucrase, maltase, and palatinase (Daileda *et al.* 2016). The purpose of this study was to determine the prevalence of selective lactase deficiency amongst a large cohort of pediatric patients undergoing esophagogastroduodenoscopy (EGD) and compare rates amongst IBD and non-IBD patients. A secondary aim of this study was to evaluate the rates of sucrase, maltase, and palatinase deficiencies in the same cohort.

Materials and Methods

Patient Selection

All cases of upper endoscopic evaluation by two physicians at Texas Children's Hospital between April 2010 and August 2016 were collected from the PedsCORI database (Thakkar *et al.* 2007). The indications for which EGDs were pursued within these patients included abdominal pain, nausea/vomiting, weight loss, failure to thrive, dysphagia, diarrhea, history or concern for celiac disease, history or concern for IBD (Table 1). Hospital records for these patients were reviewed and mucosal enzyme levels were recorded if obtained. Associated demographic data including age, sex, and race/ethnicity were also extracted and evaluated. The protocol was approved by the Baylor College of Medicine Institutional Review Board (IRB # H40484)

Mucosal enzyme analysis

Mucosal biopsies were obtained from the proximal duodenum during time of EGD and samples were sent to and analyzed at the Children's Hospital of Buffalo certified laboratory. The enzyme activity levels were reported in μM/min/g protein with normal reference levels of >15 μM/min/g protein for lactase, >25 μM/min/g protein for surcease, >100 μM/min/g protein for maltase and >5.0 μM/min/g protein for palatinase. Specific disaccharidase levels were recorded, and patients were determined to be disaccharidase deficient based on the normal reference range. Given that secondary (non-specific) disaccharidase deficiency may occur from microvillous damage, patients were only categorized as lactase, or selective disaccharidase deficient, if all other disaccharidases were normal.

Table 1. Primary indications for endoscopic evaluation amongst all study subjects greater than 9 years of age.

Primary Indication for Endoscopy	Number of Patients (% of total)
Abdominal pain	110 (34.5%)
IBD	40 (12.5%)
Nausea/vomiting	38 (11.9%)
Reflux symptoms	32 (10.0%)
Other	23 (7.2%)
Weight loss	22 (6.9%)
Celiac disease	18 (5.6%)
Diarrhea	18 (5.6%)
Failure to thrive	6 (1.9%)
Eosinophilic esophagitis	3 (0.9%)
Dysphagia	3 (0.9%)
Anemia	2 (0.6%)
Bleeding	2 (0.6%)
Barrett's esophagus	1 (0.3%)
Infection	1 (0.3%)

Table 2. Race distribution across patients.

Race/Ethnicity	Number of Patients
Caucasian	326
Hispanic	105
Asian	51
African American	46
American Indian	2
Unknown	30

Statistical Analysis

Unpaired Student T-test was performed for group comparisons. Fischer exact test was used to compare overall rate of lactase deficiency amongst non-IBD patients and IBD patients and to compare rates of lactase deficiency between patients of different races. A p-value of <0.05 was used for determining statistical significance.

Results

A total of 739 charts were examined. Of the 739 patients, 560 underwent mucosal enzyme testing at the time of their EGD. The median age of all patients was 11 years with a range of 0.17 years to 19 years. The most common primary indications for endoscopic evaluation included abdominal pain, history of IBD, nausea/vomiting, reflux symptoms, and weight loss (Table 1). The majority of patients were Caucasian (58%). (Table 2). The overall rate of lactase deficiency was 39% (220/560). There was a statistically significant negative correlation between age and lactase level ($R= -0.158$, $p=0.00017$) (Figure 1).

The youngest patient found to have selective lactase deficiency was 1 year of age. No statistically significant correlation was seen between levels of sucrose, maltase, or palatinase with age. One patient underwent endoscopy at multiple time points with corresponding mucosal enzyme testing done at the same time. The results showed an expected decline of lactase levels with increasing age (49.7 μM/min/g at 1 year of age, 18.5 μM/min/g at 4 years of age, 8 μM/min/g at 8 years of age). When the study population was divided by primary indications for endoscopy, no significant difference was seen in lactase levels amongst the various groups.

There was significant variation in the rate of selective lactase deficiency when comparing Caucasian patients with patients of other races (Figure 2). Lactase deficiency was most common among African American and Asian patients (65% and 57%,

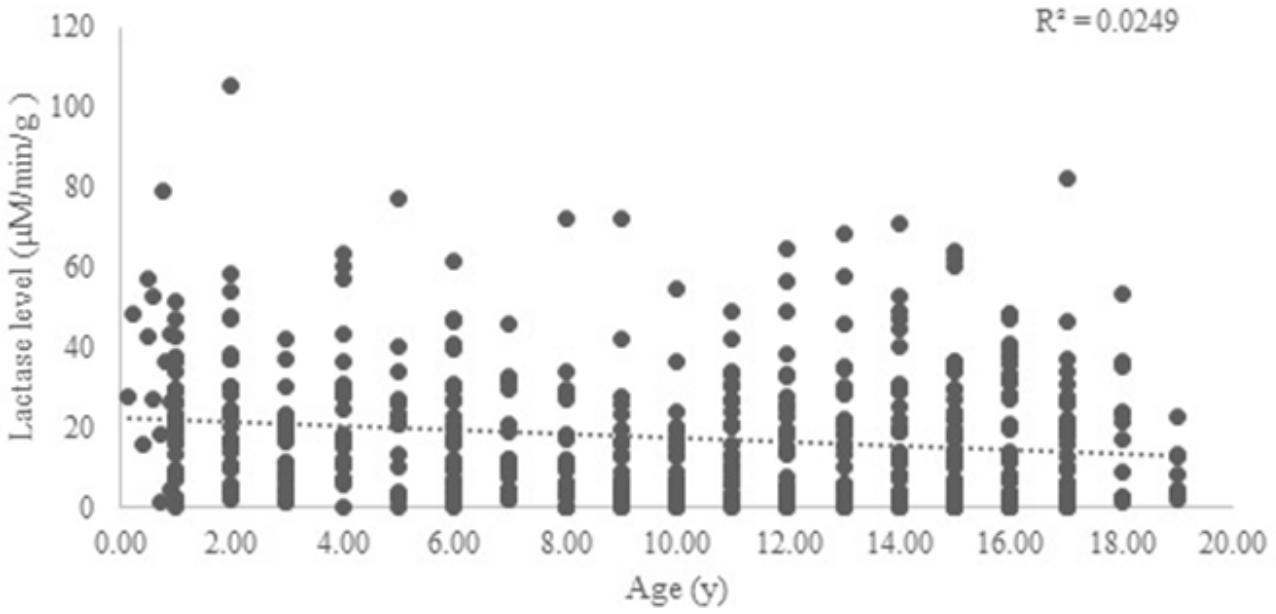


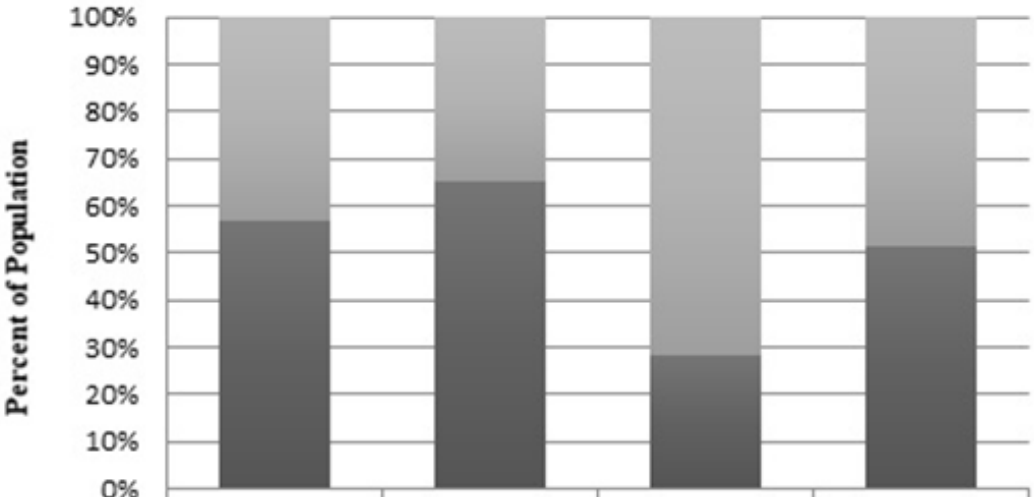
Figure 1. Correlation between age and lactase levels. Lactase levels had a significant negative correlation with age (R= -0.158 p= 0.00017).

respectively). These rates were significantly higher than the rate of lactase deficiency amongst Caucasian patients (28%, p<0.0001). For the cohort of Hispanic patients, 51% were found to have selective lactase deficiency, again significantly higher than that of Caucasian patients (p<0.0001). There was no significant difference in rates of selective lactase deficiency between the non-caucasian ethnic subgroups. The average lactase level of patients within each ethnic group under the age of 5 was also compared to help elucidate whether patients of certain ethnic groups may simply be born with lower levels of lactase. Within this age group, there was a significant race dependent variation in lactase levels (Figure 3; p=0.0078). Under age 5, Hispanic and African American children had the lowest average lactase levels (14.8 and 13.9, respectively). Additionally, within this age group, there was a statistically significant difference in average lactase levels when comparing the Asian and Hispanic patient population (p=0.003); Caucasian to Hispanic population (p=0.003); Asian to African American (p=0.0023); and the African American to Caucasian populations (p=0.03) (Figure 3).

The rates of selective deficiencies of the other disaccharidases were also examined. Four (0.71%) patients had selective maltase deficiency with ages ranging from 0.4 years to 9 years. None of these patients had a diagnosis of IBD. Three of these patients underwent EGD for nausea/vomiting while one patient underwent EGD for poor weight gain. No selective sucrase or palatinase deficient patients were identified. There were a total of 57 patients who were found to have pan-DD. Of these patients, 10 had a diagnosis of IBD. There was no significant difference in the proportion of pan-DD amongst the IBD group as compared to the non-IBD group (13.9% vs. 9.6%, p=0.29).

In order to examine the prevalence of lactase deficiency in IBD patients, the overall cohort of our study was divided into those with a diagnosis of IBD (CD, UC, or IBD unclassified [IBDU]) and those without a diagnosis of IBD. The median age of IBD patients was higher than the non-IBD patients (designated as controls within this sub-analysis). Therefore, in order to remove age related lactase level bias in the analysis, all patients under the age of 10 years were excluded from final statistical analysis when comparing IBD to the non-IBD groups. The resulting two groups after this age correction both had a median age of 11 years (p=0.51). The overall rate of lactase deficiency in this population of patients was 43%. The rate of lactase deficiency amongst the IBD group was slightly higher (45%) as compared to the non-IBD controls (42%), but not significantly (p=0.68) (Table 3). Average lactase, sucrase, maltase, and palatinase levels were also similar between the two groups (Table 4).

The rate of lactase deficiency amongst the CD specific IBD sub-group was also determined and compared to the non-IBD controls. Though the rate of lactase deficiency was higher among the CD patients compared to non-IBD (50% vs. 42%), this difference was not statistically significant (p=0.41). Similarly,



	Asian	African American	Caucasian	Hispanic
Non-lactase deficient	22	16	234	51
Lactase Deficient	29	30	92	54

Figure 2. Distribution of lactase deficiency by patient race. There was a significant ($p=7.56x10^{-11}$) race dependent variation in lactase activities by ANOVA. Fischer exact testing for Asian to African American (p=0.4144), Asian to Caucasian (p<0.0001), Asian to Hispanic (p=0.6086), African American to Caucasians (p<0.0001), Black to Hispanic (p=0.1544) and Caucasians to Hispanic (p<0.0001).

there was no statistically significant difference in the rate of lactase deficiency in CD patients when compared to patients with UC (50% vs. 37% respectively, p=0.41).

Discussion

Lactase deficiency can be a significant cause of GI discomfort within the pediatric population. Furthermore, within the pediatric IBD population, lactase deficiency may mimic the symptoms of a disease flare. Disaccharidase testing, however, is not a routine aspect of IBD monitoring and care. Neither is lactose restriction. The purpose of this study was to evaluate the rate of selective lactase and other DD among IBD patients as compared to that of non-IBD patients who underwent EGD evaluation in a large pediatric gastroenterology practice. Previous studies

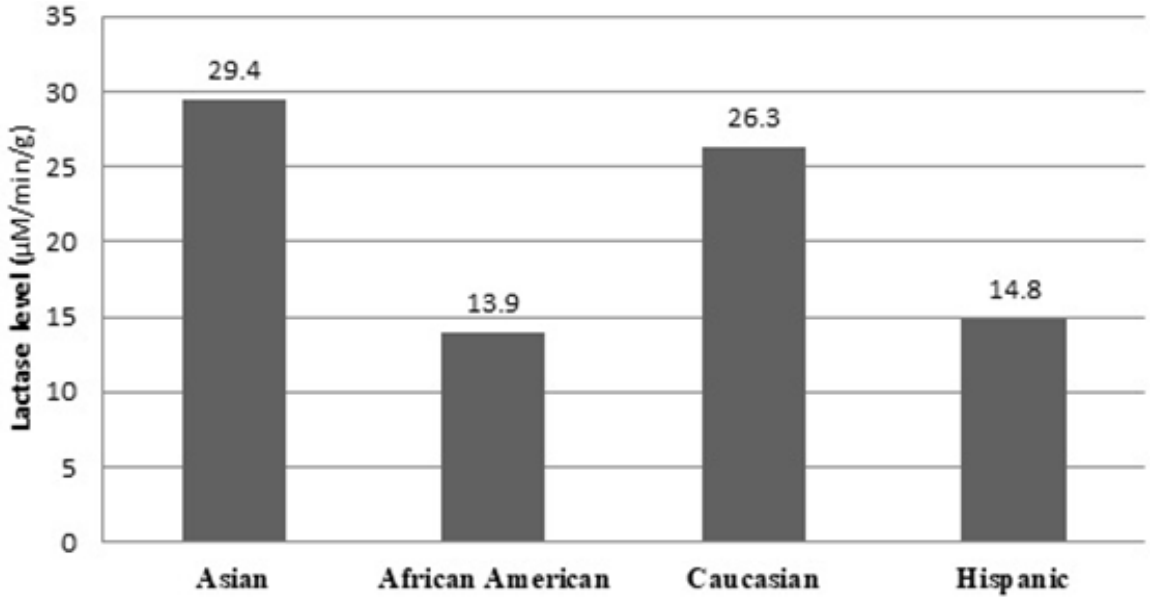


Figure 3. Average lactase levels in patients younger than age 5 amongst various ethnic groups (N= 25 in Hispanic group; N=68 in Caucasian group; N=14 in Asian group). Again, there was a significant (p=0.0078) race dependent variation in lactase levels by ANOVA. Student T testing for Asian to African American (p=0.023), Asian to Caucasians (p=0.291), Asian to Hispanic (p=0.003), African American to Caucasians (p=0.030), African American to Hispanic (p=0.405) and Caucasians to Hispanic (p=0.003).

Table 3. Rates of lactase deficiency in all patients greater than 9 years of age, IBD versus non-IBD.

	Median Age (range)	Number of Males	Number of Females	Rate of selective lactase deficiency
All patients	14 yrs (10-19)	141	179	43%
Non-IBD	14 yrs (10-19)	101	153	42%
IBD	14 years (10-19)	40	26	45%

making this comparison within the pediatric population have limited their control population to those patients with abdominal pain (Pfefferkorn *et al.* 2002). This work is unique by its large sample size (560 total patients) and by the examination of patients with any indication for upper endoscopic evaluation, not just abdominal pain.

The finding of an overall 39% lactase deficiency within our study population is consistent with previous studies on lactase deficiency in the pediatric population (Daileda *et al.* 2016). This high rate of lactase deficiency supports that testing for DD in children with indication for EGD should be considered. Given that no significant difference was seen in lactase levels by presenting symptomatology, a high level of suspicion should hold for all pediatric GI patients towards lactase deficiency. The most recent cost of the disaccharidase panel was $208 (http://www.pedsgiwny.com/gi-lab.html). As comparison, the same laboratory charged $41 for fecal pancreatic elastase testing. Based on this information, we recommend careful cost/benefit calculation to consider maximizing the value of an already indicated invasive procedure (EGD) in the vulnerable pediatric population by examining disaccharidase levels with a rather high (~39%) diagnostic yield.

Although the rate of selective lactase deficiency was higher in the IBD population (45%), this was not found to be statistically significant when corrected for age. This lack of correlation between IBD and lactase deficiency is consistent with a study by Pfefferkorn *et al.* (2002). Although CD would be expected to have greater small bowel involvement and possible secondary lactase deficiency, there was no significant difference between CD and UC patients in this respect. This supports the idea that lactase deficiency in IBD patients is not a result of mucosal inflammation, but can be a separate and common entity, which should be evaluated for at first endoscopic assessment if possible.

Although histologic inflammation was not specifically examined in this study, previous work has been inconclusive in regards to the relationship between histologic inflammation and disaccharidase activity. Some studies showed lack of correlation between disaccharidase activity and histopathologic findings, while others found an inverse relationship between these measures (Gupta *et al.* 1999, Harrison & Walker-Smith 1977, Shulman *et al.* 1991, Tori *et al.* 2007). To eliminate incidence of secondary pan-disaccharidase deficiency due to microvilli destruction, patients with concurrent maltase, sucrase, or palatinase deficiency were excluded when calculating rates of lactase deficiency in this study. Of the study population, 57 (10.2%) were found to have pan-DD. Interestingly, there was no significant difference in rates of pan-DD when comparing IBD patients with non-IBD patients (p=0.29). This seems to suggest that the inflammation associated with IBD may not result in higher incidence of pan-disaccharidase deficiency secondary to microvillous destruction.

Although no significant difference in rates of lactase deficiency was seen in IBD versus non-IBD patients, the results of this study did show a significant difference in rates of lactase deficiency between various ethnic groups when compared to Caucasian patients. The highest rates were found in African American and Asian patients (65% and 57%, respectively), while Caucasian patients had the lowest rate of lactase deficiency (28%). Similar results were seen in a Finnish study comparing children of Finnish descent to children of African descent (Kolho & Savilahti, 2000). Likewise, in one adult British study, the rate of lactase deficiency was found to be higher in non-Caucasian patients when compared to Caucasian adults (Ferguson *et al.* 1984). Although adult studies have shown these ethnic differences in rates of lactase deficiency, the results of our work indicate that similar differences exist within the pediatric population and adds knowledge about the higher levels of lactase deficiency in Hispanic children compared to Caucasians. It is of interest to note that previous work

Table 4. Average disaccharidase levels amongst the IBD versus non-IBD groups.

	Average Lactase level	Average Sucrase level	Average Maltase level	Average Palatinase level
IBD	14.3	52.3	153.0	10.8
Non-IBD	15.9	54.4	157.2	11.2
P-value	p=0.47	p=0.55	p=0.63	p=0.65

by Kirschner *et al.* (1981) noted an increased rate of lactose malabsorption as determined by lactose breath hydrogen test within the Caucasian Jewish population as compared to Caucasian non-Jewish population. Given the retrospective nature of our study, a similar comparison was not able to be made using tissue mucosal enzyme studies to determine how the proportion of Jewish patients may have influenced our results. Therefore, this question would be worthwhile to examine in the future.

It is also unclear whether children of certain ethnicities are simply born with lower levels of lactase, or whether they lose enzyme activity at a faster rate, or a combination of the two. To address this question, we compared average lactase levels amongst patients under 5 years of age within each ethnic group. There was significantly lower average lactase level in young Hispanic children compared to Asians or Caucasians. This suggests that Hispanic children may be born with lower lactase levels as compared to their Asian and Caucasian counterparts. In the meantime, Asian children may lose lactase activity at a higher rate than Caucasians, since they are more commonly lactase deficient than Caucasians later in childhood. However, the small sample size within each ethnic group below age 5 was relatively low for this comparison (Figure 3: N=25 in Hispanic group; N=68 in non-Hispanic Whites group; N=14 in Asian group). Therefore, these questions should be further addressed in larger groups of children before a final conclusion can be brought. Nevertheless, our results argue for having a higher clinical suspicion for lactase deficiency and consequent malabsorption symptoms in non-Caucasian pediatric patients.

A weakness of this retrospective study is the lack of data regarding symptomatology of the patients at the time of mucosal biopsy. As studies in irritable bowel syndrome (IBS) have shown, there is a difference between lactose malabsorption and lactose intolerance. Patients may lack adequate enzymatic activity for the breakdown of lactose, but may not show signs or symptoms of lactose intolerance (von Tirpitz *et al.* 2002). Previous studies have also revealed increased rates of reported milk intolerance in CD as compared to healthy controls, even though there was no significant difference in measured duodenal lactase enzyme levels (von Tirpitz *et al.* 2002). A study to determine if IBD patients may benefit from a lactose free diet secondary to perceived milk intolerance despite normal duodenal lactase activity would be important to perform in the future.

In IBD patients, symptoms of abdominal pain and diarrhea often trigger concerns for a potential flare. The symptoms of lactase deficiency, however, can have many similarities to that of IBD flares. The results of this work argue that potential lactase deficiency should be considered in these patients. Though not significantly different from the non-IBD patient population, lactase deficiency occurs at relatively high rate within the IBD patients. Studies have shown that lactose exposure may have an effect on colonic microflora (Szilagyi *et al.* 2010). This may have as of yet unknown consequences on colonic inflammation and the course of IBD. The rate of other selective DDs (maltase, sucrase, and palatinase) appears to occur at a negligible rate amongst the IBD population, arguing against routine elimination of these disaccharides from the diet. There is no doubt that IBD patients often have significant nutritional difficulties secondary to chronic inflammation. The decision to counsel for a complete avoidance of all lactose containing products is a significant one, especially given the higher risk of osteopenia amongst this group. Screening via mucosal biopsy can therefore be an important first step prior to making such impactful dietary modifications.

Conflicts of interest

The authors declare no conflicts of interest.

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Authorship Statement

Richard Kellermayer is the guarantor of this manuscript and the work detailed within this submission. Dr. Annie Goodwin contributed to this work as the primary author of the paper in addition to data gathering. Dr. Richard Kellermayer was the primary investigator and initator of this work and contributed writing and editing of the final manuscript. Dr. Lina Karam and GS Gopalakrishna contributed to this work via data collection and editing of the final manuscript. All authors approved the final version of this manuscript.

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