



Molecular Detection of Norovirus and Sapovirus in Pediatric Patients with Acute Gastroenteritis in Chiang Mai, Thailand

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Abstract

Norovirus and sapovirus are significant causes of acute gastroenteritis, which remains a major illness leading to morbidity and mortality in children worldwide, including Thailand. This study investigated the prevalence of norovirus and sapovirus infections in children under 5 years old who were hospitalized with acute gastroenteritis in Chiang Mai, Thailand during 2021–2022. Furthermore, the genotype characteristics of these viruses were examined. A total of 616 stool samples were screened for norovirus by real-time PCR, while conventional PCR was employed for sapovirus detection. The virus genotypes were then characterized by nucleotide sequencing. The results demonstrated that 15.42% were positive for norovirus and 1.62% were positive for sapovirus. Comparing 2021 and 2022, the norovirus infection rate increased from 10.89% to 19.81%. In this study, nine genotypes of norovirus were identified (GII.2, GII.3, GII.4, GII.6, GII.7, GII.8, GII.10, GII.17, and GII.21). The most predominant genotype was GII.4 (26.64%), followed by GII.2 (20.29%), GII.3 (15.94%), and GII.17 (14.49%). Notably, GII.2 and GII.17 exhibited higher detection rates compared to several previous studies in Thailand. For sapovirus, the detection rate in 2021 was 0.66%, but in 2022 it was increased to 2.56%. Three genotypes of sapovirus were detected, with GI.1 being the most prevalent (66.67%), followed by GI.8 (22.22%), and GI.6 (11.11%). To the best of our knowledge, this is the first report of sapovirus genotypes GI.8 and GI.6 in Thailand. In conclusion, norovirus and sapovirus remain highly significant viral pathogens causing acute gastroenteritis in children in Thailand. Hence, it is imperative to maintain continuous monitoring and surveillance.

Keywords: *Gastroenteritis, Diarrhea, Norovirus, Sapovirus, Molecular Techniques*

1. Introduction

Acute gastroenteritis remains responsible for high levels of morbidity and mortality in the general population, particularly for at-risk groups, such as infants and young children, the elderly, and immunocompromised individuals (Flynn, Olortegui, & Kosek, 2024). The majority of acute gastroenteritis cases in humans are caused by virus infections. Among these, the caliciviruses, including norovirus and sapovirus, have been reported as the most important etiologic agents (Schmitz et al., 2023). Norovirus and sapovirus are classified as members of the family *Caliciviridae*. The viruses are small and nonenveloped with a linear, positive-sense, single-stranded RNA genome of approximately 7.4 kb in length. They can be spread from person to person through fecal-oral routes. Infection can lead to severe diarrhea, causing stomach pain, vomiting, and nausea. Currently, there is no vaccine available for preventing norovirus and sapovirus infections.

As cultivation of norovirus in cell cultures remains challenging, clinical symptoms and molecular techniques are primarily utilized for diagnosis and genetic characterization of the virus. Real-time reverse transcription-polymerase chain reaction (real-time RT-PCR) and reverse transcription-polymerase chain reaction (RT-PCR) methods are commonly used for calicivirus detection (Oka et al., 2015; Wasielewski et al., 2024).

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A meta-analysis spanning from 2015 to 2020 and encompassing studies from 45 countries globally revealed that the overall prevalence of norovirus infection in pediatric patients with acute diarrhea was about 17% (Farahmand et al., 2022). Norovirus is currently divided into at least 10 genogroups (GI to GX). Each genogroup is further subdivided into several genotypes, and a total of 49 genotypes have been identified. The norovirus GI and GII are mainly associated with human disease (Chhabra et al., 2019). Among norovirus genotypes, norovirus GII.4 is the most prevalent genotype detected in humans and has been identified in many countries, including Thailand (Khamrin et al., 2022). For sapovirus, a review article of the burden of diarrheal disease caused by sapovirus in many countries demonstrated that the prevalence of sapovirus infection during 2014–2020 varied from 1 to 17% (Becker-Dreps, González, & Bucardo, 2020). Sapovirus is divided into 19 genogroups (GI-GXIX), of which GI, GII, GIV and GV infect humans. The sapovirus GI and GII are commonly detected in pediatric patients with acute gastroenteritis, whereas GIV and GV are seldom reported as associated with human infection. Currently, at least eight genotypes of GI, five of GII, and one each of GIV and GV have been identified. Among sapovirus genotypes, sapovirus GI.1 is the genotype most predominantly detected in humans (Oka, Wang, Katayama, & Saif, 2015).

For norovirus and sapovirus distributions in Thailand, the overall prevalence of norovirus infection in patients with acute gastroenteritis across all age groups ranged from 0.1% to 44.7%, while that of sapovirus ranged from 0.0% to 15.0%. The majority of norovirus genogroups detected were norovirus GII, with norovirus GII.4 being the most predominant genotype, followed by GII.3. Moreover, sapovirus genogroups GI, GII, GIV, and GV were found to be circulating in Thailand (Kumthip, Khamrin, & Maneekarn, 2018).

Thus, the aim of this study was to investigate the prevalence of norovirus and sapovirus infections, through the potential use of molecular techniques, in children hospitalized with acute gastroenteritis in Chiang Mai, Thailand from 2021 to 2022.

2. Objectives

- 1) To investigate the prevalence of norovirus and sapovirus infection among pediatric patients hospitalized with acute gastroenteritis in Chiang Mai, Thailand using molecular techniques.
- 2) To identify norovirus and sapovirus genotypes circulating in pediatric patients hospitalized with acute gastroenteritis in Chiang Mai, Thailand.

3. Materials and Methods

3.1 Specimen collection

A total of 616 stool samples were collected from children who were admitted with acute gastroenteritis in five hospitals in Chiang Mai province, Thailand including Maharaj Nakhon Chiang Mai Hospital, Sriphat Medical Center, Sansai Hospital, Sanpatong Hospital, and Rajavej Chiangmai Hospital during January 2021 to December 2022. The inclusion criteria were the inpatients who had sudden passages of loose or watery stools more than three times per day for less than 14 days with the exclusion of bloody stools. The ages of the patients ranged from neonate up to 5 years old. All stool samples were stored at -20 °C until use. The study was conducted with the approval of the Institutional Research Ethics Committee of the Faculty of Medicine, Chiang Mai University (MIC-2557-02710), and written informed consent was obtained from the participants' guardians. The sample size was calculated using the following formula:

$$n = \frac{Z^2 p(1 - p)}{e^2}$$



In this equation, n is the number of samples required for this study, Z is the confidence level (95%), p is the approximate prevalence rates of norovirus and sapovirus infections from a previous study in Chiang Mai, Thailand between 2019 to 2020 (0.187 and 0.009 for norovirus and sapovirus, respectively) (Phengma et al., 2022), and e is the precision level (0.05). It was indicated that 234 samples were minimally required for the study of norovirus infection, whereas 14 samples were minimally required for the study of sapovirus infection.

3.2 Norovirus and sapovirus detections

The viral RNA genome was extracted from the supernatant of 10% fecal suspension in phosphate-buffered saline (PBS) pH 7.4 using a Geneaid Viral Nucleic Acid Extraction Kit II (Geneaid, Taipei, Taiwan) according to the manufacturer's protocol. The viral RNA was reverse transcribed into cDNA following the manufacturer's instructions (Thermo Fisher Scientific, Waltham, MA, USA). The presence of noroviruses GI and GII were detected by real-time PCR, while sapovirus was detected by conventional PCR as previously described (Phengma et al., 2022).

3.3 Genotype identification by nucleotide sequence analysis

All the norovirus GI and GII, plus the sapovirus strains detected in our study were further characterized for their genotypes by nucleotide sequencing (First BASE Laboratories Sdn Bhd, Selangor Darul Ehsan, Malaysia). The obtained nucleotide sequences were analyzed using the ClustalX and the BioEdit software programs and then compared with those of the reference strains available in the GenBank database using the Basic Local Alignment Search Tool (BLAST) server (<http://blast.ncbi.nlm.nih.gov/Blast.cgi>). Moreover, the obtained sequences were also analyzed using the Human Calicivirus Typing Tool (<https://calicivirustypingtool.cdc.gov/bctyping.html>) to confirm their genotypes with the results from the BLAST analysis.

3.4 Statistical analysis

The differences in norovirus and sapovirus infection rates between different age and gender groups were analyzed by IBM SPSS version 22 and the Z-score calculator software. The Chi-square test and Fisher's exact test were used, with the significance level set at $p < 0.05$, indicating statistical significance.

4. Results and Discussion

4.1 Results

4.1.1 Prevalence of norovirus and sapovirus infections

From a total of 616 stool samples collected from 2021 to 2022, norovirus and sapovirus were detected at 15.42% (95/616 samples), and 1.62% (10/616 samples), respectively. The norovirus GII was detected as the most predominant genogroup at 14.93% (92/616 samples), while norovirus GI was detected at 0.49% (3/616 samples). As shown in Table 1, the infection rate of both norovirus and sapovirus increased significantly in 2022 compared to 2021. In 2021, 33 out of 303 (10.89%) samples were positive for norovirus, while only two out of 303 (0.66%) samples were positive for sapovirus. However, in 2022, 62 out of 313 (19.81%) tested positive for norovirus, and eight out of 313 (2.56%) tested positive for sapovirus.

Table 1 Prevalence of norovirus and sapovirus infections in children with acute gastroenteritis in Chiang Mai, Thailand (2021–2022)

Year of study	No. of specimens tested	No. of norovirus positive (%)	No. of genogroup positive (%)		No. of sapovirus positive (%)
			Norovirus GI	Norovirus GII	

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2021	303	33 (10.89)	2 (0.66)	31 (10.23)	2 (0.66)
2022	313	62 (19.81)	1 (0.32)	61 (19.49)	8 (2.56)
Total	616	95 (15.42)	3 (0.49)	92 (14.93)	10 (1.62)

4.1.2 Prevalence of norovirus and sapovirus infections in children with various age groups and genders

A total of 616 pediatric patients were enrolled in this study. Of these, 348 and 247 were male and female, respectively, and 21 were those without available gender information. The patients were also categorized into different age groups (Table 2).

Table 2 Characteristics of children infected with norovirus and sapovirus

Patient information	No. of specimens tested	No. of norovirus positive (%)	No. of sapovirus positive (%)	p-value	
				norovirus ^a	sapovirus ^b
Gender					
Male	348	55 (15.80)	5 (1.44)	0.996	0.748
Female	247	39 (15.79)	5 (2.02)		
N/A ^c	21	1 (4.76)	0 (0.00)		
Age (years)					
0–1	237	25 (10.55)	2 (0.84)	0.031	0.097
>1–2	132	25 (18.94)	4 (3.03)		
>2–3	50	10 (20.00)	3 (6.00)		
>3–4	42	11 (26.19)	1 (2.38)		
>4–<6	39	8 (20.51)	0 (0.00)		
N/A ^c	116	16 (13.79)	0 (0.00)		

^a Norovirus was analyzed by Chi-square test (significance level at 0.05)

^b Sapovirus was analyzed by Fisher's exact test (significance level at 0.05)

^c N/A: The information was not available

It was found that the prevalence of norovirus and sapovirus infections was not statistically different between male and female children (p-value = 0.996 for norovirus, p-value = 0.748 for sapovirus). When comparing the norovirus infection rate between each age group, it was found that the infection rate was dependent on age (p-value = 0.031). The highest prevalence of norovirus infection was observed in children



aged more than 3 to 4 years old. However, norovirus infection rates between other age groups were not significantly different. For sapovirus, the infection rates in all age groups were not significantly different (p -value = 0.097) (Table 2).

4.1.3 Distribution of norovirus and sapovirus genotypes

For norovirus GI genotype characterization, one of each of three different genotypes of norovirus GI, including GI.4, GI.5, and GI.6, were identified. For norovirus GII, GII.2, GII.3, GII.4, GII.6, GII.7, GII.8, GII.10, GII.17, and GII.21 were detected. The major genotypes of norovirus GII were GII.4 (24.64%), followed by GII.2 (20.29%), GII.3 (15.94%), GII.17 (14.49%), GII.6 (10.14%), GII.7 (7.25%), GII.10 and GII.21 (each at 2.91%), and GII.8 (1.45%) (Table 3). However, for the remaining 26 samples that were positive for norovirus based on real-time PCR, their VP1 region could not be amplified. This was probably due to the low viral load in the samples. It was observed that the norovirus samples with VP1 regions that could not be amplified had cycle threshold (Ct) values higher than 35. For sapovirus, each of three different genotypes were found in this study, including GI.1, GI.6, and GII.8. The GI.1 was the most predominant genotype (66.67%), followed by GII.8 (22.22%), and GI.6 (11.11%). In the remaining single sample that tested positive for sapovirus using RT-PCR, its VP1 also could not be amplified.

Table 3 Distribution of norovirus and sapovirus genotypes detected in acute gastroenteritis in children in Chiang Mai, Thailand (2021–2022)

Genotype	Year of study		Total (%)
	2021	2022	
Norovirus GI			
GI.4	1	0	1 (33.33)
GI.5	1	0	1 (33.33)
GI.6	0	1	1 (33.33)
Norovirus GII			
GII.2	7	7	14 (20.29)
GII.3	2	9	11 (15.94)
GII.4	3	14	17 (24.64)
GII.6	4	3	7 (10.14)
GII.7	4	1	5 (7.25)
GII.8	0	1	1 (1.45)
GII.10	2	0	2 (2.90)
GII.17	1	9	10 (14.49)
GII.21	0	2	2 (2.90)
Sapovirus			
GI.1	0	6	6 (66.67)
GI.6	1	0	1 (11.11)
GII.8	0	2	2 (22.22)

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4.2 Discussion

Acute gastroenteritis is a widespread infectious disease that can potentially lead to severe dehydration in vulnerable populations, such as young children. Norovirus and sapovirus are significant causes of acute gastroenteritis in humans (Schmitz et al., 2023).

The epidemic occurrence of norovirus in Chiang Mai, Thailand from 2019 to 2020 was 18.7% (Phengma et al., 2022), which closely approximates the global infection rate observed from 2015 to 2022 at 17.7% (Farahmand et al., 2022). Interestingly, the infection rate of norovirus in this study is slightly lower (15.42%) than that reported in the previous study conducted in 2019–2020 (18.7%). Comparison between 2021 and 2022 showed that the norovirus infection rate increased from 10.89% to 19.81%. Particularly in 2021, there was a significant decrease of the norovirus infection rate to 10.89%. The main factor of the decrease in the infection rate may be attributed to the outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV-2). Since March 2020, Thailand has experienced the COVID-19 outbreak. To reduce transmission, the government implemented measures such as promoting the use of face masks, emphasizing hand hygiene, practicing physical distancing, and discouraging social gatherings (Rajatanavin et al., 2021). As a result of these measures, the chances of other infectious viruses spreading have decreased as well. The decline of norovirus infection during the COVID-19 outbreak was also reported in other countries such as Brazil and Germany (Jacobsen et al., 2024; Sarmiento et al., 2024).

The global detection rate of sapovirus is much lower than that of norovirus (Razizadeh, Khatami, & Zarei, 2022). The prevalence of sapovirus in this study is considered to be low, with an infection rate of 1.62%. This finding is consistent with previous studies in Chiang Mai, Thailand in 2010 to 2020, which also reported low infection rates ranging from 0.9% to 1.6% (Kumthip, Khamrin, Ushijima, Chen, Li, & Maneekarn, 2020; Phengma et al., 2022).

Since the 1990s, the norovirus Genogroup II Genotype 4 (GII.4) has been the predominant strain detected globally (Tran, Trainor, Nakagomi, Cunliffe, & Nakagomi, 2013). Between 2015 and 2020, the average global prevalence of norovirus GII.4 infection was approximately 59% (Farahmand et al., 2022; Kendra et al., 2022). Consistent with the findings from other reports worldwide, norovirus GII.4 was also the predominant genotype in this study. In addition, the remaining three genotypes were also commonly identified, including GII.2 (20.29%), GII.3 (15.94%), and GII.17 (14.49%). It is notable that the detection rates of norovirus GII.2 and GII.17 have increased compared to the previous research conducted in the same area (Phengma et al., 2022). This is in line with those reported from several other countries worldwide.

Regarding norovirus GII.2, Thailand experienced an outbreak of this genotype in Chiang Mai, Bangkok, and Khon Kaen provinces from 2016 to 2017 (Supadej et al., 2019; Thanusuwannasak et al., 2018). During the same period, outbreaks of GII.2 were also observed in several countries in Asia and Europe (Bidalot et al., 2017; Cheung et al., 2019; Niendorf et al., 2017; Thongprachum et al., 2017). However, the detection of this genotype was found to be only 0.1% in Chiang Mai, Thailand from 2005 to 2015 (Supadej et al., 2017). In the years 2019 to 2020, GII.2 slightly increased with the detection rate of 5.5% (Phengma et al., 2022). However, in our study, there was a sudden increase to 20.29% from 2021 to 2022. For norovirus GII.17, this genotype began emergence in Bangkok and Khon Kaen provinces, Thailand, with 11.6% in 2015 (Thanusuwannasak et al., 2018). In another study in Bangkok, Khon Kaen, Phitsanulok, and Saraburi from 2017–2018, the prevalence of norovirus GII.17 was 16.2% (Chuchaona et al., 2019). In contrast, the detection of this genotype was found to be only 0.8%–1.6% in Chiang Mai, Thailand from 2017 to 2020 (Khamrin et al., 2022; Phengma et al., 2022). Nevertheless, in this study, norovirus GII.17 abruptly increased to 14.49%.

Based on the genotype identification of norovirus GI in the years 2021–2022, three genotypes were sporadically detected, including GI.4, GI.5, and GI.6 (each with one strain). These genotypes are considered



to be the common globally detected genotypes, including in Thailand (Farahmand et al., 2022; Khamrin et al., 2024).

Among the sapovirus detected in our study, sapovirus GI.1 was the most frequently identified genotype, followed by GII.8 and GI.6, respectively. It is noteworthy that the GII.8 and GI.6 genotypes were detected for the first time in Thailand. From the literature review, the sapovirus GII.8 was first identified in 2008 in Peru, followed by outbreaks in China in 2019 (Liu et al., 2016; Yan et al., 2020). Regarding GI.6, it has been sporadically found in Japan, China, and Botswana (Chan-It et al., 2012; Jiao et al., 2023; Makhaola et al., 2022).

The benefit of knowing the genotype of norovirus and sapovirus circulating in Chiang Mai, Thailand may be useful for vaccine development in the future. The limitations of this study were that the study was conducted only in Chiang Mai province and only a two-year period was surveyed. The study should be performed over a long-term period and expanded to other provinces of Thailand.

5. Conclusion

Our results revealed that norovirus and sapovirus were the important viral pathogens that caused acute gastroenteritis in children hospitalized with diarrhea in Chiang Mai, Thailand from 2021 to 2022. It was observed that several norovirus and sapovirus genotypes were circulating in this area. Continuous surveillance is therefore crucial for understanding the complexity of norovirus and sapovirus genetic variations and to monitor the emergence of new genotypes.

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