
ORIGINAL RESEARCH**THE CLINICAL EPIDEMIOLOGY OF NOROVIRUS INFECTION IN CHILDREN WITH DIARRHEA AT REGIONAL PUBLIC HOSPITAL DR.SOETOMO***Epidemiologi Klinis Infeksi Norovirus Pada Penderita Diare Anak di Rumah Sakit Umum Daerah Dr. Soetomo***Alpha Fardah Athiyah¹** , **Sofia Wardhani¹**, **Andy Darma¹** , **I Gusti Made Reza Gunadi Ranuh¹** , **Dadik Raharjo²** , **Toshiro Shirakawa³** , **Subijanto Marto Sudarmo¹** ¹Department of Child Health, Dr. Soetomo Hospital, Faculty of Medicine Universitas Airlangga, Surabaya 60132, Indonesia, alpha-f-a@fk.unair.ac.id²Indonesia-Japan Collaborative Research Center for Emerging and Re-emerging Infectious Diseases, Institute of Tropical Disease, Universitas Airlangga, Surabaya 60286, Indonesia, dadik_tdc@yahoo.co.id³Division of Infectious Diseases, Department of International Health, Kobe University Graduate School of Health Science, Kobe 654-0142, Japan toshiro.shirakawa@gmail.comCorresponding Author: Alpha Fardah Athiyah, alpha-f-a@fk.unair.ac.id, Department of Child Health, Dr. Soetomo Hospital, Faculty of Medicine Universitas Airlangga, Surabaya 60132, Indonesia

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ABSTRACT**Background:** Norovirus has become a major cause of severe outbreaks of gastroenteritis since the discovery of the rotavirus vaccine, with the main symptom being diarrhea. Until now, research on the epidemiological analysis of norovirus has not been carried out at Regional Public Hospital (RSUD) Dr. Soetomo, Surabaya.**Purpose:** This study aims to provide clinical epidemiology data and an analysis of norovirus infections in children with diarrhea at Regional Public Hospital (RSUD) Dr. Soetomo, Surabaya, Indonesia, including the prevalence of norovirus infection in each age group and sex, its clinical appearance, and its seasonal variation. **Methods:** A cross-sectional study was conducted in children aged 1–60 months hospitalized for diarrhea in RSUD Dr. Soetomo between April 2013 and March 2014. Identification of the virus in the stool was done by norovirus enzyme immunoassay Quick NaviTM Noro2. The proportion, age, sex, clinical symptoms, and patterns of the norovirus seasonal data were calculated. **Results:** Norovirus was detected in 64 samples (19%) of the 340 stool samples, with a mean patient age of 11.75 months; it was mostly found in patients less than 24 months of age (95%), and 64% were male. The monthly pattern of norovirus infection was mostly found in November, followed by May and April. The clinical symptoms were fever (72%), vomiting (66%), bloating (59%), abdominal cramps (34%), perianal inflammation (27%), abdominal distension (16%), and seizures (8%). **Conclusion:** The prevalence of norovirus was found to be high in patients with diarrhea aged 1–60 months hospitalized in RSUD Dr. Soetomo, with a proportion of 19%. Further research is needed to determine the severity of norovirus infection.

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ABSTRAK

Latar Belakang: *Norovirus merupakan penyebab utama wabah gastroenteritis berat dengan gejala utama diare setelah ditemukannya vaksin rotavirus. Penelitian tentang analisis epidemiologi norovirus hingga saat ini belum dilakukan di rumah sakit Dr. Soetomo. Tujuan:* Penelitian ini bertujuan untuk memberikan data epidemiologi klinis dan analisis infeksi norovirus pada anak diare di Rumah Sakit Umum Daerah (RSUD) Dr. Soetomo, Surabaya, Indonesia, termasuk prevalensi infeksi norovirus pada setiap kelompok umur dan jenis kelamin, gambaran klinisnya, dan variasi musimnya. **Metode:** Studi cross-sectional dilakukan pada pasien rawat inap diare usia 1-60 bulan di rumah sakit Dr. Soetomo antara bulan April 2013 - Maret 2014. Identifikasi virus pada feses menggunakan enzyme immunoassay *Norovirus Quick NaviTM Noro2*. Perhitungan data dilakukan untuk mengetahui besar proporsi infeksi norovirus, usia penderita diare, jenis kelamin penderita diare, gejala klinis dan pola musim norovirus. **Hasil:** Norovirus terdeteksi positif pada 64 sampel (19%) dari 340 feses, dengan usia rata-rata 11 – 12 bulan (11,75 bulan), sebagian besar ditemukan pada penderita diare usia kurang dari 24 bulan (95%) dan 64% penderita berjenis kelamin laki-laki. Pola infeksi norovirus bulanan, kebanyakan ditemukan pada bulan November, diikuti oleh bulan Mei dan April. Gejala klinisnya adalah demam 72%, muntah 66%, kembung 59%, kolik abdomen 34%, radang perianal 27%, distensi abdomen 16%, dan kejang 8%. **Kesimpulan:** Prevalensi norovirus ditemukan cukup tinggi pada pasien diare rawat inap usia 1-60 bulan di RSUD Dr Soetomo dengan proporsi 19%. Perlu dilakukan penelitian lebih lanjut untuk menentukan derajat keparahan infeksi norovirus.

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INTRODUCTION

Norovirus has become an important etiology of acute diarrhea in children since the rotavirus vaccine was successfully implemented in children under five years old (Da Costa et al., 2017). Norovirus was found in 1970 as a 27-nm-long, single-strand, non-enveloped Ribonucleic acid (RNA) virus and is classified under the family Caliciviridae. Norovirus gastroenteritis is often associated with diarrhea outbreaks during wintertime and, in a closed community such as a cruise, is transmitted sporadically from person to person (Weinberg, 2019). Norovirus is also accused of being the culprit of more than 14,000 hospitalized patients, 281,000 visits to emergency departments, and 627,000 visits to outpatient clinics every year in American children aged <5 years old. Furthermore, it is responsible for

70,000–200,000 deaths in various age groups every year (Bányai, Estes, Martella, & Parashar, 2018). Unfortunately, to the best of our knowledge, epidemiological studies on norovirus are still limited in Indonesia. This study aims to provide clinical epidemiology data and an analysis of norovirus infections in children with diarrhea at Regional Public Hospital (RSUD) Dr. Soetomo, Surabaya, Indonesia, including the prevalence of norovirus infection in each age group and sex, its clinical appearance, and its seasonal variation.

METHODS

Population and Sample of Study

This study was a cross-sectional study. The population was all babies and children aged 1–60 months old hospitalized in the pediatric department of RSUD Dr. Soetomo, Surabaya, with

the chief complaint of diarrhea and diagnosed with acute gastroenteritis. All samples that agreed to follow this study had to give informed consent. A total of 340 fecal samples were collected from April 2013 to March 2014 and analyzed in the Institute of Tropical Disease (ITD), Universitas Airlangga, Surabaya. The exclusion criteria for this study were subject was not collecting their fecal samples, and the fecal sample was too small to be analyzed. Ethical clearance was given by the Ethics Committee of RSUD Dr. Soetomo, Surabaya (number 188/Panke.KKE/VIII/2012).

Fecal Sample Analysis and Questionnaire

The subjects were interviewed and examined in order to obtain information on their age, sex, seasonal variation, abdominal distention, duration and frequency of diarrhea, duration and frequency of vomiting, body temperature, seizure episodes, perianal redness, bloating, increased bowel sounds, dehydration status, and nutritional status. Fecal samples were collected using ± 10 -ml rectal tubes by medical personnel and stored at -80°C . The samples were analyzed in ITD for norovirus identification using enzyme immunoassay Norovirus Quick Navi™ Noro2. The serum electrolytes were measured in subjects who were norovirus-positive.

Norovirus Identification

The identification of norovirus in this study was via enzyme immunoassay Quick Navi™ Noro2, containing anti-norovirus genogroup I (GI) monoclonal antibody (rat) and anti-norovirus GII monoclonal antibody (rat) dissolved in Sample Quick Navi Suspension (for fecal samples). Preservatives were made from buffer additives-surfactant and 0.08 w/v% sodium azide. The specificity was 92.00%, and the sensitivity was 98.30%. Serum electrolytes, such as sodium, chloride, potassium, and calcium, were measured by taking 3 ml blood in an Enthylene Diamine Tetra Asetat (EDTA) tube.

Data Analysis

The data from the questionnaire were analyzed using descriptive analysis. The data will be presented as the mean and standard deviation.

RESULTS

A total of 418 subjects were obtained, but 78 were excluded. From the 340 samples included in this study, 64 samples were norovirus-positive. From those 64 samples, rotavirus was positive in

four samples, while 41 samples were *Escherichia coli* (*E. coli*)-positive, 22 samples were *Klebsiella pneumoniae*-positive, and one sample was positive for *Enterobacter aerogenes*. The mean age of patients who were norovirus-positive was 11.75 months, of which 95% consisted of children under 24 months old. Meanwhile, the mean age of patients who were norovirus-negative was 13.22 months, of which 82.60% also consisted of children under 24 months old.

Seasonal Variation

In this study, the highest numbers of patients with diarrhea who were norovirus-positive were observed in November ($n = 19$), May ($n = 12$), and April ($n = 10$). This seasonal variation can be seen in Figure 1.

Sex and Nutritional Status

The subjects who were norovirus-positive were 64% male ($n = 41$) and 36% female ($n = 23$). The subjects who were norovirus-negative were 56.88% male ($n = 157$) and 43.12% female ($n = 119$). The nutritional status of patients who were norovirus-positive was 76.56% normal ($n = 49$), 14.06% moderately undernourished ($n = 9$), and 9.38% severely undernourished ($n = 6$).

Signs and Symptoms

Approximately 94% ($n = 60$) of subjects who were norovirus-positive suffered from acute diarrhea, while the remaining 6% ($n = 4$) suffered from persistent diarrhea. In subjects who were norovirus-negative, acute diarrhea was experienced by 97.50% ($n = 269$), and persistent diarrhea was experienced by 2.50% ($n = 7$). The most common symptoms found in subjects who were norovirus-positive were vomiting, fever, abdominal pain, and seizure. Common signs found in patients who were norovirus-positive were bloating, abdominal distention, increased bowel sounds, and perianal redness. The frequency of those signs and symptoms is shown in Tables 1 and 2. The consistency of the fecal samples that were norovirus-positive was 79.70% ($n = 51$) watery stool, 15.60% ($n = 10$) mushy stool, 3.10% ($n = 2$) bloody stool, and 1.60% ($n = 1$) mucoid stool. Severe dehydration was found in 5% ($n = 3$) of the subjects; 92% ($n = 59$) of subjects were found to have moderate dehydration, and 3% ($n = 2$) of subjects were not dehydrated.

In the norovirus-negative group, the consistency of the fecal samples was 69.40% ($n = 192$) watery stool, 19.80% ($n = 54$) mushy stool, 1% ($n = 3$) bloody stool, and 9.80% ($n = 27$)

mucoid stool. Severe dehydration was found in 10.50% (n = 29) of the subjects; 88% (n = 243) had moderate dehydration, and 1.40% (n = 4) did not have dehydration. In this study, all subjects were discharged with improvement. No subjects died during the study.

Serum Electrolyte

In this study, the sodium, potassium, and chloride levels in most of the patients who were norovirus-positive were within the normal limit.

DISCUSSION

This study revealed positive norovirus infection in 64 subjects (19%) out of the 340 samples. Norovirus is commonly found in children aged 6–12 months and less commonly found in children aged 24 months or older (Ranuh et al., 2019). A previous study showed that the

prevalence of norovirus infection in children with diarrhea was 25.50% in patients under six months old and tended to decrease with age; the lowest prevalence was found in children aged 3–5 years old and was only around 11.50% (Chung et al., 2017).

In this study, the mean age of the subjects who were norovirus-positive was 11.75 months. Most subjects (95%) who were norovirus-positive were less than 24 months old (the highest incidence was in children aged 12 months old), and the remaining 5% were aged 25–60 months old. Another study by Fernández, Ulloa, Meneses, Matiz, & Gutiérrez (2015) conducted in Colombia showed that rotavirus infection in children aged 0–3 months and norovirus in children aged 4–6 months usually cause diarrhea, which means that norovirus commonly attacks children under 24 months old.

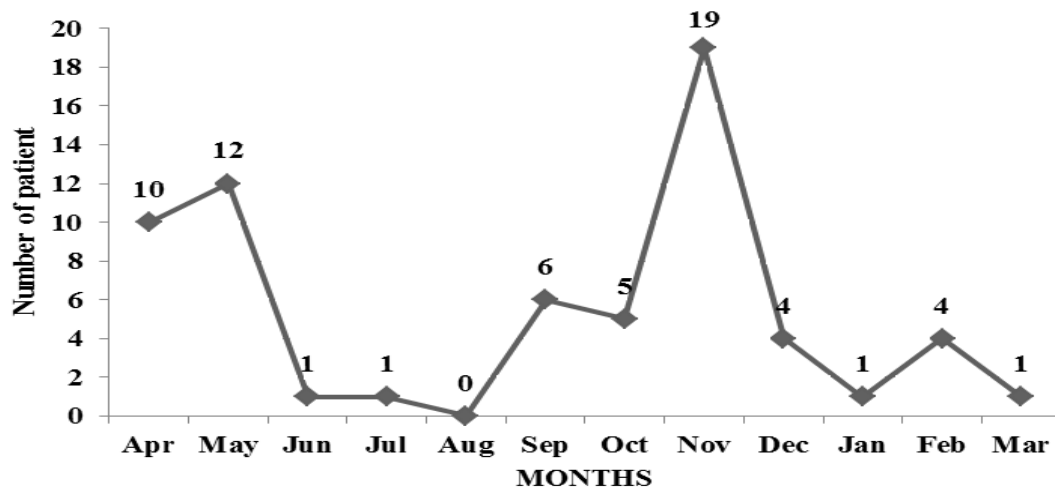


Figure 1. Seasonal variation of norovirus infection in children with diarrhea at RSUD Dr. Soetomo, April 2013–March 2014 (n = 64)

Table 1

Clinical appearance of positive norovirus and negative norovirus infection

| Signs and symptoms | Positive Norovirus | | Negative Norovirus | |
|------------------------|--------------------|--------|--------------------|--------|
| | (Σ) | (%) | (Σ) | (%) |
| Fever* | 46 | 71.88 | 155 | 56.16 |
| Vomitus* | 42 | 65.63 | 191 | 69.20 |
| Bloating* | 38 | 59.38 | 159 | 57.61 |
| Inconsolable cry* | 22 | 34.38 | 132 | 47.83 |
| Increased bowel sound* | 20 | 31.25 | 84 | 30.43 |
| Anus merah* | 17 | 26.56 | 50 | 18.12 |
| Abdominal distention* | 10 | 15.63 | 42 | 15.22 |
| Seizure* | 5 | 7.81 | 36 | 13.04 |
| Bloody diarrhea* | 2 | 3.13 | 3 | 1.09 |
| Total | 64 | 100.00 | 276 | 100.00 |

*1 patient may experience more than one symptom

Table 2

Duration and Frequency of Each Clinical Manifestation of Positive Norovirus and Negative Norovirus Infection

| Clinical Manifestation | Positive Norovirus | | | Negative Norovirus | | |
|-----------------------------------|--------------------|---------|------|--------------------|---------|------|
| | Mean | Range | SD | Mean | Range | SD |
| Duration of diarrhea (days) | 3.20 | (1-14) | 2.42 | 2.93 | (1-30) | 3.14 |
| Frequency of diarrhea (times/day) | 5.79 | (1-20) | 3.56 | 3.37 | (1-25) | 2.49 |
| Duration of vomiting (days) | 1.33 | (0-8) | 1.57 | 2.71 | (1-14) | 1.86 |
| Frequency of vomiting (times/day) | 2.64 | (0-10) | 2.79 | 2.19 | (1-14) | 1.83 |
| Duration of fever (days) | 2.03 | (0-10) | 2.15 | 2.13 | (1-14) | 1.05 |
| Body temperature (°C) | 37.44 | (36-40) | 0.70 | 37.72 | (36-41) | 0.97 |
| Length of stay (days) | 4.45 | (1-26) | 5.00 | 3.91 | (1-30) | 3.82 |

The result of this study is contradictory to a study from Qatar showing that norovirus infection is mostly found in children aged 1–3 years old (Mathew et al., 2019). Meanwhile, a similar result was seen in a study about the prevalence of acute gastroenteritis in children under five years old that stated that norovirus infection most commonly occurs in children 12–23 months old, while rotavirus infection, on average, occurs at 17 months old (Guarino et al., 2014). Research by Mohamed, Hameed, & Al-Rubai (2016) also showed that norovirus is the most dominant enteric virus in children under five years old, followed by rotavirus in children under one year old.

Most episodes of diarrhea happen within the first two years of life. The highest incidence occurs in the six- to 12-month age group. This phenomenon elicits the effects of decreasing maternal antibodies and inadequate immune response in that specific age group. When unhygienic complementary food is given and babies start to crawl, contact with bacteria and other contaminants results in diarrhea. After two years of age, episodes of diarrhea will decline along with the development of active immunity (Robilotti, Deresinski, & Pinsky, 2015).

In this study, norovirus was detected all year long, except in August. The highest numbers of cases with positive norovirus were found in November ($n = 19$), May ($n = 12$), and April ($n = 10$). A meta-analysis on the seasonal variation of norovirus showed that in the northern part of the globe, norovirus is highest in December–February, while in the southern part of the globe, norovirus is highest in June–August (Guarino et al., 2014). In a study conducted by Kim, Byeon, Lee, Jeong, & Eun (2016) also stated that norovirus was commonly identified in November–December and was not seen with other viruses.

Norovirus infection exists throughout the year. During the winter, norovirus infection

correlates with rain, which serves as an important factor for transmission, such as transmission through the water and transmission from close contact when people tend to gather together inside buildings when it is raining. In this study, it was shown that norovirus infection is found to be highest in December–February, which is the rainy season in Indonesia. An outbreak of this virus is often found in hospitalized patients following this climate pattern. Most events happen in November–April and will increase in January–March (Cardemil, Parashar, & Hall, 2017).

Rain is an important factor that plays a role in transmitting norovirus. A rise in the rainfall level will increase the risk of transmission. Outbreaks of norovirus are usually seen from fall to winter, around January to March. During winter 2014, norovirus strain GII.P17-GII.17 appeared to be the culprit of gastroenteritis outbreaks in China and Japan (de Graaf et al., 2018). This fact implicitly indicates that rainwater changes the viral load of norovirus, and thus, transmission of norovirus becomes much easier (Sözen, Gönen, & Beydilli, 2014).

In this study, four patients came in with the chief complaint of persistent diarrhea, of which three of them were severely undernourished. A study by (Attia et al (2016) involved 79 children with severe malnutrition, and 23% of these children were experiencing diarrhea. Patients of a younger age with more severe malnutrition usually die. Marasmus causes a higher mortality rate than kwashiorkor. However, four out of six severely undernourished patients require hospitalization for more than seven days. This fact is similar to the results of a research study by Iskandar, Sukardi, & Soenarto (2015) stating that episodes of diarrhea in severely undernourished patients are significantly correlated with their length of stay but do not correlate with the severity and duration of the diarrhea itself. Another study by Bhatnagar,

Kumar, Dua, Basu, & Kumar (2019) showed that the length of stay for malnourished children with diarrhea is, on average, three days longer than that for malnourished patients without diarrhea. There is a bidirectional relationship between diarrhea and malnutrition. This reciprocal relationship has long been known—on the one hand, diarrhea can cause malnutrition, and, on the other hand, malnutrition can be a risk factor for diarrhea. Every episode of diarrhea can cause malnutrition because of anorexia and malabsorption, i.e., a reduced ability to absorb nutrition, and eventually affect long-term growth and development. Meanwhile, malnutrition can cause diarrhea due to the atrophy of intestinal villi (enteropathy). Malnutrition can affect the duration of diarrhea. Around 10% of children in developing countries suffer from severe malnutrition. In this situation, deficiency of macro- and micronutrients could magnify the duration and severity of diarrhea. Malnutrition also increases the mortality rate of patients with diarrhea. Whilst norovirus infection is self-limited and short in duration, immuno-compromised patients experience longer and more severe diarrhea (Green, 2014).

Based on clinical manifestations, this study showed that norovirus infection is commonly seen as acute diarrhea with watery stool. Other signs and symptoms were vomiting, fever, and signs of lactose intolerance, such as bloating, inconsolable crying, perianal redness, and abdominal distention. Another study on norovirus showed that patients with norovirus infection frequently come in with the chief complaint of vomiting instead of diarrhea. Cases of vomiting without diarrhea are not unusual. Research by Kirby, Streby, & Moe (2016) stated that vomiting is an important symptom that should be considered in diagnosing norovirus infection. A study by Robilotti, Deresinski, & Pinsky (2015) mentioned that norovirus infection can be manifested as diarrhea, vomiting, abdominal pain, and fever—self-limited and short in duration. On average, symptoms persist only for two days. Around 86.40% patients show clinical improvement after 1–3 days. A complication that often happens is only mild to moderate dehydration.

This study also found manifestation of seizures in five subjects (7.80%), of which two subjects were hypernatremic and three subjects were accompanied by febrile seizures. A study by Kim, Byeon, Lee, Jeong, & Eun (2016) mentioned that there is a relationship between norovirus infection and seizure. Seizures in patients with norovirus infection usually happen at early onset

and for a longer duration compared to those who experience seizures due to rotavirus infection. This can be explained by the fact that fecal samples of patients with norovirus infection contain 100 billion viral particles per gram of feces, which is 10 times higher than the fecal samples of patients with rotavirus infection. The transmission of norovirus to the brain is not known exactly, but it is suspected that norovirus can infect dendritic cells, a type of cell that actively migrates from tissues to lymph nodes. In this study, subjects' seizures might have been induced by hypernatremia and a history of febrile seizures (Robilotti, Deresinski, & Pinsky, 2015).

Patients with watery diarrhea excrete sodium, chloride, and bicarbonate ions along with the excretion of their stool, causing dehydration, metabolic acidosis, and hypokalemia. Dehydration can be either isotonic, hypertonic, or hypotonic. In this study, the electrolyte status of patients with norovirus infection was either hyperchloremia or hypernatremia, which might have been caused by excessive salt consumption. Hypochloremia and hyponatremia can result from excessive fluid loss through vomiting and diarrhea (Robilotti, Deresinski, & Pinsky, 2015). The manifestation of bloating, perianal redness, inconsolable crying, and abdominal distention indicates the presence of carbohydrate intolerance in norovirus infection. Further tests should be conducted before drawing an absolute conclusion.

In this study, there were also two patients with bloody diarrhea. During colonoscopy, the patients were diagnosed with allergic colitis. Based on a previous study by Nakajima et al (2014), sporadic viral gastroenteritis usually does not show serious manifestation, though in some cases bloody stool could be present.

This was a pilot study reporting on the clinical epidemiology of norovirus infection in patients with diarrhea at the pediatric department of RSUD Dr. Soetomo. The prevalence of norovirus infection was 19%. This result highlights the significance of norovirus as one of the etiologies of diarrhea in babies and children, especially in countries where the rotavirus vaccine has successfully eradicated rotavirus infection.

Research Limitations

The enzyme immunoassay kit used in this study was limited to norovirus genotypes GI and GII.

CONCLUSION

This study reported the initial data on the clinical epidemiology of norovirus infection in babies and children with diarrhea admitted to RSUD Dr. Soetomo, Surabaya. The data obtained showed that norovirus was one of the etiologies of diarrhea in the patients aged 1–60 months old, with a prevalence of 19%. Norovirus infection should be considered as one of the possible culprits of diarrhea in children, especially in countries where the rotavirus vaccine has successfully eradicated rotavirus outbreaks.

CONFLICT OF INTEREST

All of researchers stated that there is no conflict of interest during this study.

AUTHOR CONTRIBUTIONS

All authors participate actively in this article and are responsible for the content of writing, including in preparation, draft writing, research design selection, analysis, and revision of the article. AFA: Conceptualization, Methodology, Writing- Reviewing and Editing. SW: Methodology, Visualization, Investigation. AD: Data curation, Writing- Original draft preparation. RGR : Writing- Reviewing and Editing. DR: Data curation, Software. TS: Supervision. SMS: Validation, Supervision.

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