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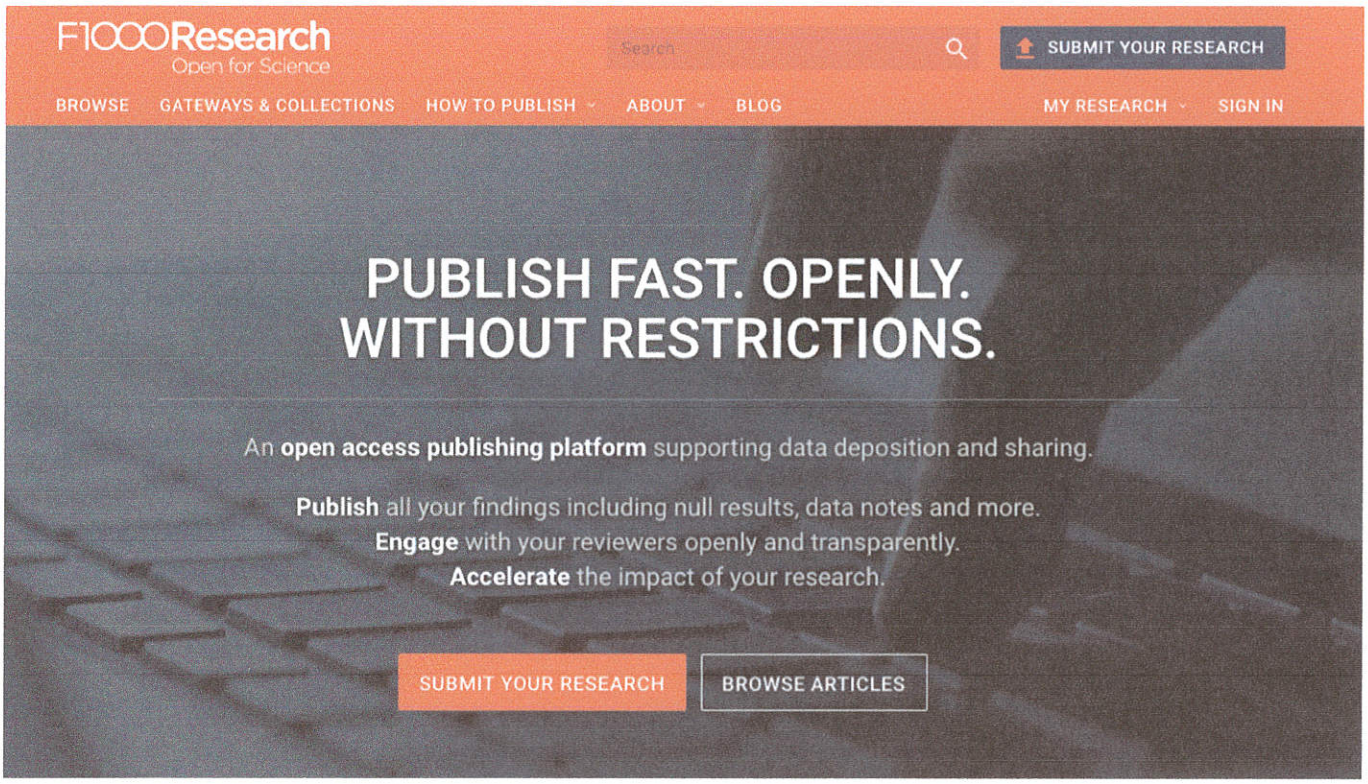

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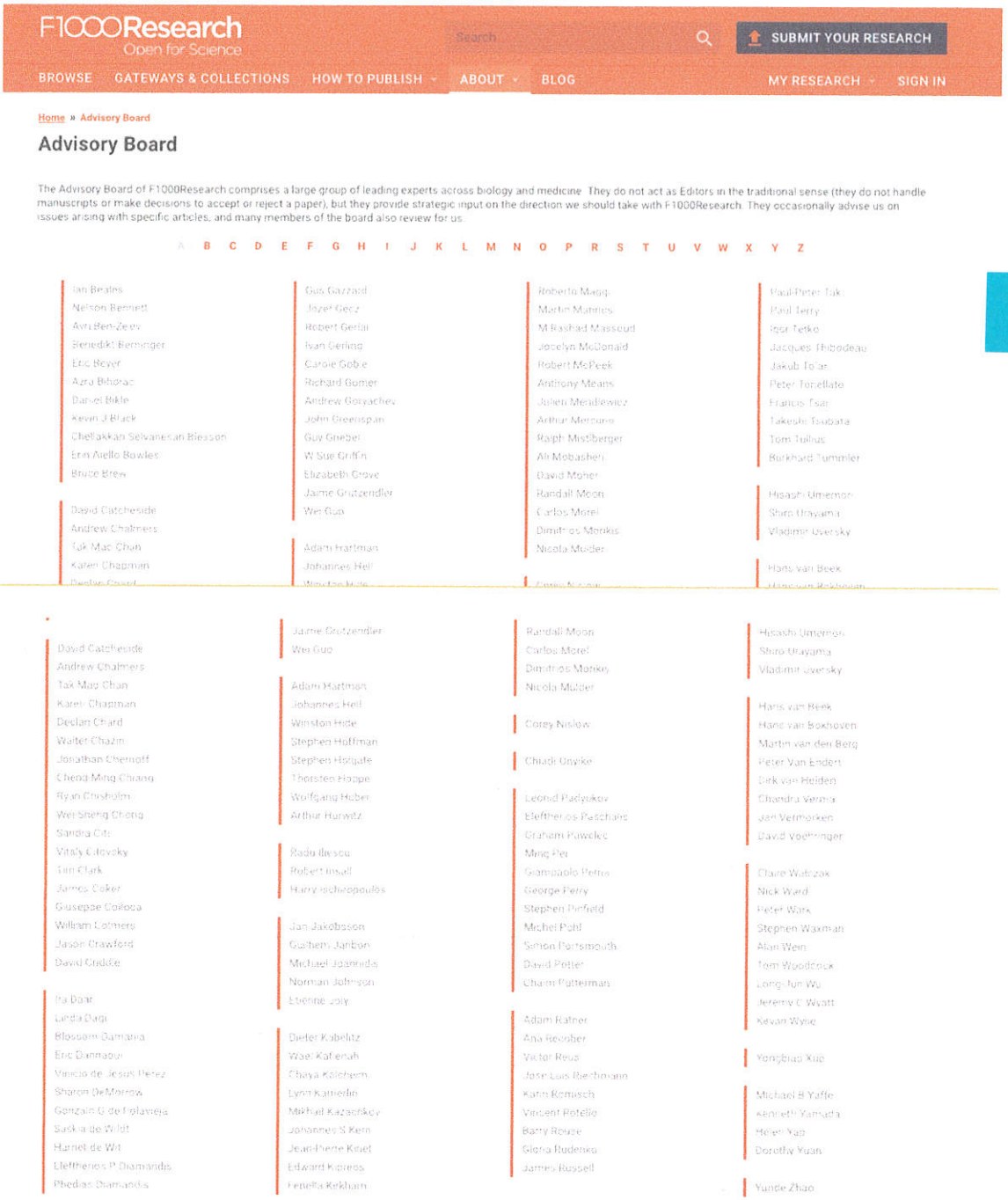

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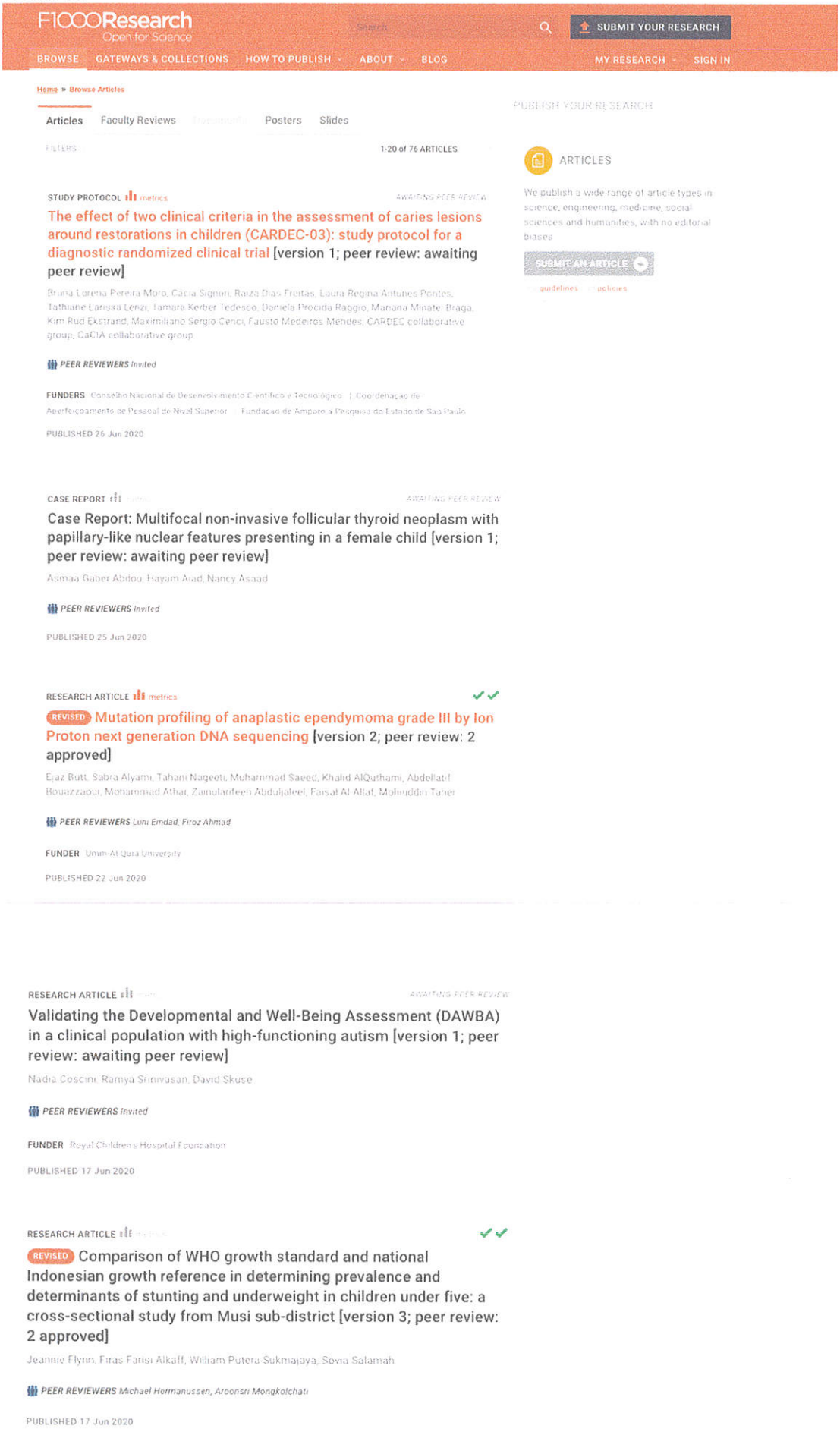
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RESEARCH ARTICLE

REVISED Clinical manifestation of norovirus infection in children aged less than five years old admitted with acute diarrhea in Surabaya, Indonesia: a cross-sectional study [version 3; peer review: 2 approved]

Alpha Fardah Athiyyah, Katsumi Shigemura, Koichi Kitagawa, Nazara Agustina, Andy Darma, Reza Ranuh, Dadik Raharjo, Toshiro Shirakawa, Masato Fujisawa, Subijanto Marto Sudarmo

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PUBLISHED 09 Mar 2020

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Case Report: Congenital absence of uvula and trismus - a rare presentation of Van der Woude syndrome [version 1; peer review: 1 approved with reservations]

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PEER REVIEWER Emmanuel Adu

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RESEARCH ARTICLE

REVISED Relationship between postpartum depression and lactation status at a Japanese perinatal center: A cross-sectional study [version 2; peer review: 2 approved]

Shunji Suzuki

PEER REVIEWERS Hiroko Iwata, Felix Emeka Anyiam

PUBLISHED 30 Jan 2020

SYSTEMATIC REVIEW

Efficacy and safety of microbiota transfer therapy for the management of autism spectrum disorder in children: a systematic review [version 1; peer review: 1 approved, 1 not approved]

Pablo Daniel Estrella Porter, Luis Eduardo Guzmán Freire, Joseth Paulina Adatty Molina, Maria Veronica Burneo Raza, Henry Alejandro Carrion Celi, Isabel Maria Espinosa Borja, Andrea Carolina Falconi Páez, Andres Sebastián Gudiño Vega, Maria José Jaramillo Cartwright, Sebastian Xavier Oña Vargas, Sebastián Eduardo Puga Martinez, Jonathan R Guillemot

PEER REVIEWERS Valerie d'Astous, Gianluca Ianiro

PUBLISHED 27 Jan 2020

RESEARCH ARTICLE

REVISED Clinical manifestation of norovirus infection in children aged less than five years old admitted with acute diarrhea in Surabaya, Indonesia: a cross-sectional study [version 3; peer review: 2 approved]

Previously titled: Norovirus genogroup correlation with acute diarrhea severity in Indonesian pediatric patients aged 1-60 months: a cross-sectional study

Alpha Fardah Athiyyah [1,2], Katsumi Shigemura [3-5], Koichi Kitagawa[4,6], Nazara Agustina[1,2], Andy Darma[1,2], Reza Ranuh[1,2], Dadik Raharjo[2,7], Toshiro Shirakawa[2-4,6,8], Masato Fujisawa[3], Subijanto Marto Sudarmo[1,2]

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Second version: 14 Feb 2020, **8**:2130 (https://doi.org/10.12688/f1000research.21069.2)
Latest published: 09 Mar 2020, **8**:2130 (https://doi.org/10.12688/f1000research.21069.3)

Abstract

Background: The objective of this study was to investigate the clinical manifestation of norovirus infection between norovirus genogroup and severity of acute diarrhea in pediatric patients at the Dr. Soetomo Hospital, Surabaya, Indonesia.
Methods: This cross-sectional study involved 31 participants aged 1-60 months admitted to the hospital with acute diarrhea from April 2012 to March 2013. Norovirus genogroups (GI and II) were identified from patient stool using reverse transcription polymerase chain reaction (RT-PCR). Severity was measured using the Ruuska and Vesikari scoring system.
Results: In total, 94 stool samples were obtained, of which 31 (19%) were norovirus positive. Norovirus GI was found in one sample with mild diarrhea. Norovirus GII was found in 30 samples (96.8%); one sample with mild diarrhea (3.3%), 20 samples with moderate diarrhea (66.7%), and nine samples with severe diarrhea (30%).

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version 2 (revision) 14 Feb 2020	? report	✓ report
version 1 20 Dec 2019	✗ report	? report

Conclusion: Norovirus GII was the most prevalent cause of acute diarrhea and 30% of the cases manifested as severe diarrhea.

Keywords
Diarrhea, Infection, Norovirus, Vesikari score

1 **Mohamad S. Hakim**, Gadjah Mada University (UGM), Yogyakarta, Indonesia

2 **Hirokazu Kimura**, Gunma Paz University, Gunma, Japan

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Fardah Athiyyah A: Conceptualization, Data Curation, Formal Analysis, Investigation, Writing – Original Draft Preparation; **Shigemura K**: Writing – Original Draft Preparation, Writing – Review & Editing; **Kitagawa K**: Writing – Original Draft Preparation, Writing – Review & Editing; **Agustina N**: Investigation; **Darma A**: Investigation; **Ranuh R**: Investigation; **Raharjo D**: Investigation, Methodology; **Shirakawa T**: Funding Acquisition, Project Administration, Supervision; **Fujisawa M**: Supervision; **Marto Sudarmo S**: Project Administration, Resources, Supervision

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REVISED **Amendments from Version 2**

We have revised the title because our number of patients is so small that we could not evaluate the correlation between G1 positive and severity of diarrheae.

Any further responses from the reviewers can be found at the end of the article

Introduction

Diarrhea is considered the second-leading cause of death in pediatric patients under the age of five with a worldwide annual mortality of 525,000 children. Diarrhea lasting for even a few days causes dehydration[1]. Viruses from the genus *Norovirus* from the family *Caliciviridae* are the second-leading cause of acute diarrhea after rotavirus in all age groups of pediatric patients[2–4]. Norovirus is responsible for 218,000 pediatric deaths (<15 years old) every year and for 1.1 million pediatric hospitalizations around the world[2]. In Indonesia, previous studies mentioned incidence rate around 17–30% in children[5–8].

Early identification of norovirus strain and genotype is vital for predicting the development of the disease and selecting the most suitable treatment. Genogroup diversity can be checked using reverse transcriptase polymerase chain reaction (RT-PCR). Norovirus is grouped into 40 viral strains, which are further classified into five different genogroups. Among them, GI and GII possess the most diverse genetic components[9]. From the previous study, Norovirus GII.2 genotypes had been the most prevalent norovirus strain in Indonesia (71.4%) followed by norovirus GII.17 (14.3%), one case was GII.4 and one case was GII.1[10].

Norovirus commonly causes mild and short-term diarrheal episodes[10]. Nonetheless, this virus can be fatal, particularly in pediatric, geriatric, and immunocompromised patients[11,12]. Norovirus patients showed more severe diarrhea compared to those without norovirus infection in pediatric patients. The type of norovirus strain and genome is thought to be related to diarrhea severity[12].

This study aimed to examine the clinical manifestation of norovirus infection in pediatric patients aged 1–60 months in the Dr. Soetomo General Hospital, Surabaya, Indonesia.

Methods

Ethical statement

The study protocol was approved by the Ethical Research Commission of Dr. Soetomo General Hospital, Surabaya, and conducted in line with the 1964 Helsinki declaration and its later amendments or research code of ethic issued by the Ministry of Research, Technology and Higher education. Written informed consent regarding participation in this study, the right to resign, stool and data collection and confidentiality of patient data was obtained and signed from all individuals' parents. Consent was requested from the patients' parents because the patients were 1–60 months old.

Study population

This cross-sectional study was conducted between April 2012 and March 2013 of all children aged 1–60 months old with acute diarrhea (described as defecation more than three times per day with change of stool consistency to loose or watery) admitted to the pediatric ward. Patients with a gastrointestinal-anatomical disorder such as Hirschsprung disease, severe systemic disease including sepsis, central nervous system infection or bronchopneumonia, a malabsorption disorder such as cow's milk allergy, or a compromised immune status were excluded from the study to avoid any bias. On the day of the patients' admission to the pediatric ward, parents were asked to participate in this study, and they agreed by signing the informed consent form. Stool samples were collected within 24 hours of patient admission with a sterile pot; approximately 3g of stool sample was taken from the middle part of the stool and delivered in no longer than three hours to the laboratory institution. Using a total sampling method, all samples collected until the end of March 2013 were studied.

Patient assessment

All subjects underwent physical examination and the participant's parents completed a questionnaire.

The patient assessment was carried out by the physicians. The patient's parents completed questions in the questionnaire regarding characteristic patient data[13]. These data were: patient's identity (age, gender, body weight, and body height); parent's identity (maternal education); history of diarrhea, which were divided into diarrhea duration (≤4 days, 5 days, and ≥6 days) and diarrhea frequency within 24 hours (1–3 times/day, 4–5 times/day, and ≥6 times/day); vomiting history, divided into vomiting duration (no vomiting, 1 day, 2 days, and more than 3 days) and vomiting frequency within 24 hours (no vomiting, 1 time/day, 2–4 times/day, and more than 5 times/day); and history of breastfeeding (not received breastfeeding, breastfeeding <6 months, and breastfeeding ≥6 months). Nutritional status was classified to either normal or malnutrition (underweight, stunted, wasted, and overweight) according to the definition by WHO[14].

All patients also underwent physical examination of axillary body temperature (°C), arterial pulse measured with a pulseoxymeter (times/minute), respiratory rate (times/minute) and inspection of the signs of dehydration based on WHO classification[15] and all results were written down in the questionnaire form. The questionnaire was then reviewed by the researchers and entered into the research database.

Norovirus diagnosis

Stool samples were delivered to the laboratory institution and kept in a deep freezer at -80°C until they were thawed at room temperature prior to RT-PCR analysis. To prevent laboratory contamination, our laboratory staff wore complete apparatuses, such as mask, coat, and gloves, throughout the process. RNA extraction was conducted in Bio Safety Cabinet. Before conducting PCR, all containers were disinfected using alcohol. A 10% stool suspension was prepared for each sample prior to RNA extraction by mixing 100µl stool sample with 100µl phosphate buffered saline

buffer (Sigma-Aldrich, St. Louis, USA) with a vortex mixer (QL System, MX-2500 Vortex Mixer, UK) for 15 seconds and then centrifuging at 13,000–15,000 rpm for 10 minutes (Microfuge 20, Beckman Coulter, Indiana Polis, USA). The supernatant (1µl) from the stool suspension was transferred into a clean test-tube and the Viral Nucleic Acid Extraction Kit II (Cat # VR100, Geneaid Biotech Ltd., New Taipei, Taiwan) was used to extract viral RNA, carried out according to the kit manufacturer's instructions. The eluted RNA from the samples was then stored in a deep freezer at -80°C until RT-PCR processing.

Reverse transcription was performed by mixing 75 picomoles of pdN6 random hexamers (Cat # 11034731001, Roche Molecular Biochemicals, Germany), 4U AMV Reverse Transcriptase (Cat # AMS.AMV007-1, AMS Biotechnology, Abingdon, UK) and 5µl of the eluted RNA and incubating at 42°C for 60 minutes. Approximately 10µl of the previous mixture was added to 5µl distilled water, 3µl Ex Taq DNA Polymerase (RR001B, Takara Bio Inc., Kusatsu, Japan) and 2µl of both forward and reverse primer. The primer pair used in this study for G1 were the G1SKF primer with nucleotide chain CTGCCCGAATTYGTAAATGA targeting nucleotide position 5342-5362 and a product size of 329 bp, and the G1SKR primer, with nucleotide chain CCAACCCARCCATTRTACA targeting nucleotide position 5652-5671 and a product size of 329 bp. The primer pair used in this study for G2 were the G2SKF primer, with nucleotide chain CNTGGGAGGGCGATCGCAA targeting nucleotide position 5058-5077 and a product size of 344 bp, and G2SKR, with nucleotide chain CCRCCNGCATRHCCRTTRTACAT targeting nucleotide position 5378-5401 and a product size of 344 bp.

PCR reaction was performed as follows. Initial denaturation was done at 94°C for 7 minutes, followed by 40 amplification cycles with Takara PCR Thermal Cycler Dice (TP600, Takara Bio Inc.). Each cycle consisted of denaturation at 94°C for 30 seconds, primer annealing at 50°C for 30 seconds for G1 or 57°C for 30 seconds for G2, extension reaction at 72°C for 45 seconds, followed by a final extension for 2 hours 24 minutes. The PCR product was then separated via gel electrophoresis in a 2% agarose gel and visualized under the UV light after ethidium bromide staining. The gel patterns were captured with Printgraph Fx Series (AE-6933FXN, Atto Corporation, Tokyo, Japan). The RT-PCR method used in this study was the one used by Rasanen *et al.* in Finland for identifying norovirus[16], which can reveal the genotype variety via nonstructural proteins within the virus[17]. RT-PCR is considered to have the highest sensitivity for diagnosing norovirus infection compared to other methods[18].

Vesikari Scoring System

The severity of diarrhea was measured using the Vesikari Scoring System (see Table 1). This severity scale was originally developed to evaluate the effectiveness of rotavirus vaccines based on 20 points[19]. The used parameters have been tested for reliability and validity in a cohort study conducted by Freedman with Cronbach's $\alpha > 0.7$.

Diarrhea severity was assessed by evaluating seven clinical symptoms, including the duration of diarrhea, diarrhea frequency within 24 hours, vomiting duration, vomiting frequency within 24 hours, body temperature, dehydration status, and treatment. From those components, we could use the modified Vesikari score[20] to assess diarrhea severity. Mild diarrhea is equal to a score of < 7; a score of 7–10 is equivalent to moderate manifestation, and severe manifestation scores > 10.

Statistical analysis

Descriptive analysis was used to determine proportions from patients' and parents' identity data (age, gender, nutritional status and maternal education variables) and clinical patient data (diarrhea type, diarrhea duration, diarrhea frequency, vomiting duration and frequency, temperature, dehydration status and

Table 1. Vesikari Scoring System.

Parameter	Score			
	0	1	2	3
Diarrhea				
Maximal no. of diarrhea episodes per 24-hour period	0	1–3	4–5	≥6
Diarrhea duration[17]	0	1–4	5	≥6
Vomiting				
Maximal no. of vomiting episodes per 24-hour period	0	1	2–4	≥5
Vomiting duration[16]	0	1	2	≥3
Temperature (°C)	<37.0	37.1–38.4	38.5–38.9	≥39
Dehydration	<5%	5–10%	>10%	
Treatment	None	Oral rehydration solution	Hospitalization	

Maximum score = 19; score <7 = mild severity; score 7–10 = moderate severity; score >10 = severe severity.

This table has been reproduced with reference to the study of Ruuska & Vesikari, 1990[19]

causative pathogen). The results of basic and clinical data are presented in tables and divided based on the PCR norovirus result (positive norovirus group and negative norovirus group).

Results

Participant characteristics

Samples were collected in the pediatric wards of the Dr. Soetomo General Hospital Surabaya. A total of 94 stool samples were acquired from eligible subjects within 11 months between April 2012 and March 2013. Of those samples, 31 (33.0%) were positive for norovirus infection using the RT-PCR method (Figure 1)[13].

The basic characteristics of all patients participated in this study are presented in Table 2. Most of the participants whose samples were positive for norovirus were male (54.8%), the youngest participant was one month old and the oldest was 24 months old. Twenty-two participants (71%) were between 6–23 months old.

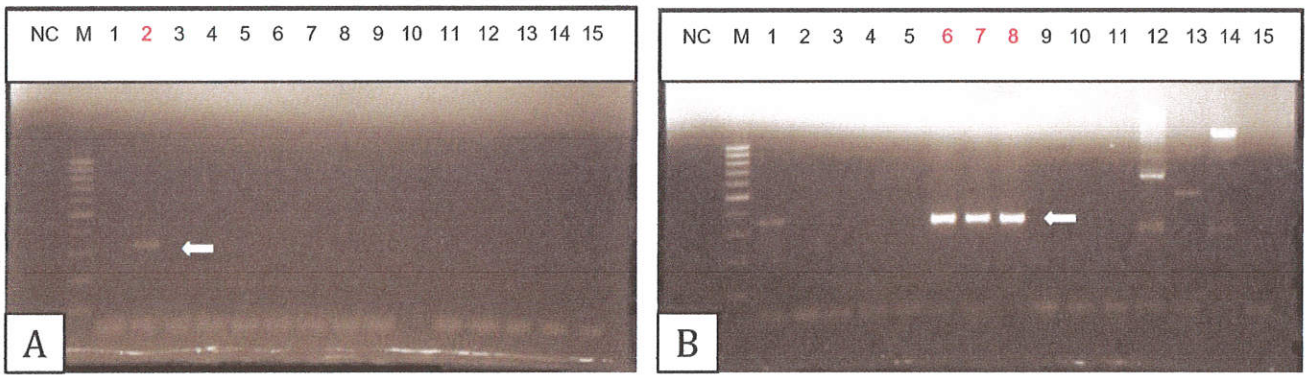

Figure 1. Results of norovirus genogroup analysis by polymerase chain reaction. A. Negative control lines (NC), marker lines (M), DNA stepladder marks (100bp). Second lines (GI, 329bp); arrow shows 300 bp marker. **B.** Negative control lines (NC), Marker lines (M), DNA stepladder marks (100bp). Sixth, seventh, and eighth lines (GII, 343bp); arrow shows 300 bp marker.

Table 2. Basic characteristics data.

Variable	Norovirus positive		Norovirus negative	
	n	%	n	%
Age (months)				
1–5	9	29.0	10	15.9
6–23	22	71.0	47	74.6
>23	0	0.0	6	9.5
Gender				
Male	17	54.8	41	65.1
Female	14	45.2	22	34.9
Nutrition status				
Normal	21	67.7	14	22.2
Malnutrition	10	32.3	49	77.8
Breastfeeding status				
Never	5	16.1	3	4.8
Breastfeeding ≤ six months	7	22.6	47	74.6
Breastfeeding ≥ six months	19	61.3	13	20.6
Maternal education				
Low	5	16.1	7	11.1
Middle	22	71.0	47	74.6
High	4	12.9	9	14.3

As for nutrition status, most of the subjects had adequate nutrition status (67.7%), while 10 subjects (32.3%) were considered malnourished. A total of 26 subjects (83.9%) were breastfed, with 19 subjects (61.3%) breastfed for more than six months and the rest (22.6%) were breastfed for under six months.

Most patients in negative norovirus group were within 6–23 months old (74.6%) and were male (65.1%). Differences were found in the nutritional status of norovirus negative patients, in whom malnutrition was more prevalent (77.8%) than in norovirus positive patients. Breastfeeding for less than six months was also more common in the norovirus negative group (74.6%).

Clinical characteristic data are presented in Table 3. On average, the subjects were brought to the hospital after suffering diarrhea for two days with a frequency of diarrhea of five times within 24 hours. Other symptoms experienced by the subjects included vomiting (71% in positive norovirus group and 63% in negative norovirus group) with the most frequent duration of vomiting being one day (14.9% in positive norovirus group and 40.4% in negative norovirus group) and the most commonly observed frequency of vomiting being 2–4 times (9.6% in positive norovirus group and 21.3% in negative norovirus group) per day.

The most frequent body temperature on admission to the hospital was below 37°C for positive norovirus group (48.4%) and sub-febrile (37.1–38.4°C) for the negative norovirus group (50.8%). Dehydration status in this study showed that two of the patients suffered from severe dehydration in both groups, while no dehydration was found only in negative norovirus group (3.2%). Watery stool diarrhea was the most frequent type of diarrhea in both positive norovirus group and negative norovirus group (80.6% and 50.4%, respectively). Bloody or mucoid stool was found only in patients of the negative norovirus group (both 9.5%).

Diarrhea severity

Based on norovirus genogroup identification from gel electrophoresis, GI was found in one sample and GII in 30 samples (96.8%). No products other than norovirus was found.

Distribution between norovirus genogroups and degree of diarrhea severity is presented in Table 4 and shows that norovirus GI was only responsible for one case of diarrhea with moderate severity. From 30 samples that tested positive for norovirus GII, GII was responsible for 20 cases (66.7%) of diarrhea with moderate severity, and nine cases (30%) of diarrhea with severe manifestation.

Table 3. Clinical characteristic data.

Variable	Norovirus positive		Norovirus negative	
	n	%	n	%
Diarrhea type				
Watery	25	80.6	34	54.0
Loose	6	19.4	17	27.0
Bloody	0	0.0	6	9.5
Mucoid	0	0.0	6	9.5
Diarrhea duration				
1–4 days	23	24.5	52	55.3
5 days	3	3.2	7	7.4
≥6 days	5	5.3	4	4.3
Diarrhea frequency				
1–3 times	13	13.8	18	19.1
4–5 times	7	7.4	25	26.6
≥6 times	11	11.7	20	21.3
Experiencing vomiting				
Yes	22	71.0	38	60.3
No	9	29.0	25	39.7
Vomiting duration				
No vomiting	9	9.6	26	26.6
1 days	14	14.9	38	40.4
2 days	2	2.1	0	0
≥3 days	6	6.4	0	0.0
Vomiting frequency				
No vomiting	9	9.6	26	27.7
1 time	7	7.6	10	10.6
2–4 times	9	9.6	20	21.3
≥5 times	6	6.4	7	7.4
Temperature (°C)				
<37.0	15	48.4	27	42.9
37.1–38.4	12	38.7	32	50.8
38.5–38.9	1	3.2	3	4.8
>39	3	9.7	1	1.6
Dehydration status				
No dehydration	0	0.0	2	3.2
Some dehydration	29	93.5	59	93.7
Severe dehydration	2	6.5	2	3.2
Causative pathogen				
Norovirus GI	1	3.2	0	0
Norovirus GII	30	96.8	0	0

Table 4. Diarrheal severity distribution by norovirus genogroup.

		Norovirus genogroup		Total
		GI	GII	
Severity	Mild (Score <7)	0 (0%)	1 (3.3%)	1 (3.2%)
	Moderate (Score 7–10)	1 (100%)	20 (66.7%)	21 (67.7%)
	Severe (Score ≥11)	0 (0%)	9 (30%)	9 (29.1%)
	Total	1	30	31

Discussion

Norovirus has been reported as be the main cause of acute diarrhea worldwide after rotavirus in all age groups of pediatric patients both in developed and developing countries[2,3]. Norovirus strain type and genome mutation are thought to correlate with the severity of the diarrhea[11]. It is important to clarify the pathogenesis of this disease to achieve better treatment for each case.

Norovirus was identified in this study in 31 out of 94 samples (33.0%), with norovirus GII in 30 samples (96.8%) and norovirus GI in one sample (3.2%). This agrees with a previous study mentioning norovirus infection was found in 30% of 102 children aged 0–15 months in Jakarta, Indonesia[5]. However, our study results showed higher norovirus infection incidence than previous studies mentioning incidence of about 17–21%[6–8].

Another study conducted in Rio de Janeiro in Brazil from 2005–2008 showed similar results; 1,087 stool samples obtained from 879 people below 20 years old and 208 people above 20 years old had norovirus in approximately 35% of the samples, and 96% of the norovirus-positive samples were GII positive[21]. A study of 165 participants in Shanghai, China, also showed high prevalence of norovirus GII infection (97.6%), with only 2.42% of those samples positive for norovirus GI[22]. These worldwide reports suggest that the most prevalent genogroup infecting humans is GII, with GI only seen in a minority of cases.

Norovirus infection, in our study, is most prevalent in 6–23 months population. Similar to other studies, this finding might be due to protection from maternal antibodies during breastfeeding for infant of < 6 months old. After 2 years of age, incidence of norovirus infection will decline due to acquired immunity[23–26].

The degree of diarrheal severity in subjects infected by norovirus GII was mostly moderate and only 30% were classified as severe. This agrees with a study carried out by Japanese group, Nakagomi *et al.*, confirming that norovirus infection could elicit a similar degree of severity to rotavirus infection[27]. Similarly, a study in Taiwan showed that norovirus caused mild diarrhea in 30.6%, moderate diarrhea in 43.9% and severe diarrhea in 25.5% of cases using the Vesikari Scoring System. Although previous study found that norovirus GII infection could lead to a more severe clinical manifestation diarrhea and vomiting compared to other genogroups, there are also wide range of severity level within the norovirus GII genogroup itself, such as that norovirus GII.4, GII.2, GII.3, GII.6, and GII.7 are associated with higher severity score[28]. However, it is still a debate whether the genogroup itself or the viral loads that associate with clinical severity[29].

In our study, unfortunately, the degree of diarrheal severity in subjects infected by norovirus GI could not be compared to the degree of diarrheal severity in norovirus GII since norovirus GI was only detected in one sample, which is not enough for comparison.

Although this study achieved its aims, there were unavoidable study limitations. First, our sample size was comparatively small compared to previous norovirus studies in other countries. We did not include neonates below 1 month old due to our limitation to reach the neonatal ward. Secondly, we found no recurrent cases in our study, and therefore we did not analyze the relationship between norovirus genogroup classification and recurrence of diarrhea. Thirdly, since all the patients that participated in this study were all being admitted to the hospital, the treatment criteria are relatively more severe. Nevertheless, our findings largely agree with previous studies in Surabaya, Shanghai, and Rio de Janeiro, as explained in our discussion above[10,20,22]. Fourth, we did not have data about other pathogens, which might be co-infecting. In addition, we could not classify the norovirus GII into genotype, and then use this genotype to infer the severity of the disease. Finally, this study only categorized norovirus genogroups by RT-PCR. We did not perform gene sequencing for norovirus RNA. We also did not include positive controls for each PCR reaction. Future studies will address these limitations.

Conclusion

This study demonstrated that norovirus was responsible for 33.0% of diarrhea cases in the study group, and norovirus GII was significantly dominant compared to norovirus GI. As many as 30% of norovirus cases had severe diarrheal manifestation, all of which were caused by norovirus GII.

Data availability

Underlying data

Harvard Dataverse: Norovirus PCR data set. https://doi.org/10.7910/DVN/KLBUOE[13].

This project contains the following underlying data:

- Norovirus PCR data set detaverse.tab (sociodemographic information and clinical findings for norovirus positive patients)
- Master data – Noro negative (1).tab (sociodemographic information and clinical findings for both norovirus negative and positive patients)
- Original PCR gel images in JPEG format

Extended data

Harvard Dataverse: Norovirus PCR data set. https://doi.org/10.7910/DVN/KLBUOE[13].

This project contains the following extended data:

- Norovirus Study Questionnaire (ENG).pdf (copy of questionnaire in English)
- Ind-Informed for Consent_norovirus.pdf (copy of questionnaire in Indonesian)

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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 3

Reviewer Report 10 March 2020

https://doi.org/10.5256/f1000research.24984.r61038

✔ **Mohamad S. Hakim**
Department of Microbiology, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University (UGM), Yogyakarta, Indonesia

The authors already addressed all my previous comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Virology, infectious diseases, immunology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 21 February 2020

https://doi.org/10.5256/f1000research.24539.r60048

? **Mohamad S. Hakim**
Department of Microbiology, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University (UGM), Yogyakarta, Indonesia

The authors already made improvements in this revised version of manuscript based on my previous comments. However, I still have some minor questions:

1. As I have stated earlier in my previous comments, the sample size is too small to perform correlation analysis because only one GI positive manifested as moderate diarrhea. The authors should then not use term "correlation" in the objective (last paragraph of introduction section), as well as in the title. How can the authors make correlation analysis if they had only one GI positive samples? Thus, the term "correlation" is not supported by their data.
   Therefore, I highly recommend to change to a more general title, such as "Clinical manifestation of norovirus infection in children aged less than five years old admitted with acute diarrhea in Surabaya, Indonesia: a cross-sectional study" or "Norovirus infection in children aged less than five years old admitted with acute diarrhea in Surabaya, Indonesia: a cross-sectional study".

2. The authors mentioned, "Genogroup diversity can be checked using immunochromatography and reverse transcriptase polymerase chain reaction (RT-PCR)". Previously I was only concerned about electron microscopy, but I just realized that is it true that genogroup diversity can also be determined by immunochromatography? Please support your statement with solid references.

3. Please change "severer" to "more severe" (in introduction section). I have mentioned this previously, but the authors did not make any changes.

4. In the Discussion, the authors mentioned, "We did not perform gene sequencing for norovirus DNA."
   Comment: Norovirus is an RNA virus, not DNA virus. Please change.

5. In the Discussion, the authors mentioned, "One of the possible contributing factors is because we did not use positive controls for our PCR; therefore our result might have high false positive result."
   Comment: high rate of false positive result mostly due to unproper **negative** control, not positive control or due to high contaminations. In contrast, positive control is employed to reduce false negative results. The best way to confirm the PCR results is by performing sequencing of some or all positive samples. The authors should modify this issue in the next revision.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Virology, infectious diseases, immunology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 17 February 2020

https://doi.org/10.5256/f1000research.24539.r60047

Hirokazu Kimura
Department of Health Science, Graduate School of Health Science, Gunma Paz University, Gunma, Japan

The authors addressed all my comments. Thus, I recommend that the revised manuscript is now suitable for indexing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Virology and Infectious Diseases.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 27 January 2020

https://doi.org/10.5256/f1000research.23188.r57998

?

Hirokazu Kimura
Department of Health Science, Graduate School of Health Science, Gunma Paz University, Gunma, Japan

The authors studied the correlation between NoV genogroup and severity of acute diarrhea in the pediatric patients with gastroenteritis at the Hospital, Surabaya, Indonesia. NoV was detected in around 20% of the patients. In many cases, GII virus was detected, while GI was detected in one case. Moreover, 30% of the patients showed severe diarrhea. Overall, the manuscript was well written, while I had some minor comments.

1. The authors only examined by RT-PCR method. Did you detect nonspecific PCR products in the amplicons? Please add it in the results.

2. How did you prevent laboratory contamination? Please provide it in the revised manuscript.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Virology and Infectious Diseases.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 29 Jan 2020

Katsumi Shigemura, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Japan

1. The authors only examined by RT-PCR method. Did you detect non-specific PCR products in the amplicons? Please add it in the results.
Response: We suggest that non-specific PCR products refer to viruses other than norovirus. If that so, there were no products other than norovirus was found.

2. How did you prevent laboratory contamination? Please provide it in the revised manuscript.
Response: To prevent laboratory contamination, our laboratory staff wore complete apparatuses, such as mask, coat, and gloves. RNA extraction was conducted in Bio Safety Cabinet. Before conducting PCR, all containers were disinfected using alcohol.

Competing Interests: We have no conflict of interest to declare.

Reviewer Report 06 January 2020

https://doi.org/10.5256/f1000research.23188.r57997

Mohamad S. Hakim
Department of Microbiology, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University (UGM), Yogyakarta, Indonesia

Summary:
Athiyyah *et al.* reported the prevalence of norovirus infection during one year study of acute diarrhea patients <5 years old admitted to Dr. Soetomo Hospital, Surabaya, Indonesia. Reports of norovirus

prevalence in children <5 years old with acute diarrhea in Indonesia are still limited. Therefore, this paper is highly important to expand the data of norovirus surveillance in Indonesia.

Comments:
However, this paper needs a major revision to improve the way of presenting and discussing the data as I recommend the following:

1. The sample size is too small to perform correlation analysis. Only one GI positively manifested as moderate diarrhea. The authors should then not use "correlation" in the objective (last paragraph of introduction section), as well as in the title, this does not make any sense. The author can change into a more general title, such as "Clinical manifestation of norovirus infection in children aged less than five years old admitted with acute diarrhea in Surabaya, Indonesia: a cross-sectional study" or "Norovirus infection in children aged less than five years old admitted with acute diarrhea in Surabaya, Indonesia: a cross-sectional study."

2. The authors mention in the introduction: "Genogroup diversity can be checked using several methods including immunochromatography, reverse transcriptase polymerase chain reaction (RT-PCR), and electron microscopy."
Comments: any supporting evidence or reference of this statement? Norovirus genogroup is based on genetic analysis, so somehow it is weird that it can be differentiated based on electron microscopy.

3. The authors did not perform comprehensive literature searching of the previous norovirus study in Indonesia. In fact, there are already some "key" publications in this field, but the authors did not include them in this manuscript.
Please thoroughly check the referenced papers to improve author statement in both introduction and discussion section[1-5].

4. Please change "severer" to "more severe" (in introduction section).

5. In the methods: Are there any specific reason to exclude <1 month baby in this study?

6. Figure 2B, lane 1. Is it considered positive or negative? Because it seems a scanty, positive band there. It looks like Figure 2A, lane 2 which is considered as positive for norovirus GI.

7. Do the authors include positive controls for each PCR reaction? The prevalence of norovirus in this study (about 32%) is higher than that of global prevalence (about 20%) in countries that did not include Rotavirus vaccination in the NIP. So the authors should ensure that a proper and valid PCR assay has been conducted. Please check: Ahmed SM *et al.* (2014)[6].

8. Figure 1 is not necessary, so please delete it.

9. The authors mention: "Of those samples, 31 were positive for norovirus infection using the RT-PCR method". Please provide the percentage of norovirus-positive samples.

10. The authors mention in discussion: "This agrees with a previous study done in healthy subjects in Surabaya, Indonesia..." This is not a match comparison, because the previous study is in healthy, asymptomatic adult subjects. The authors should check the above papers that I recommended for much better comparison of previous studies in Indonesia.

11. In the discussion, the authors should also discuss associated risk factors of contracting norovirus based on Table 2. For example, why did in your population is the most prevalent age of norovirus positive 6-23 months?

12. The authors should add discussion about different severity of norovirus infection based on different genotpe of GII norovirus. Although they did not perform genotype identification in this study, the readers of this paper should still be aware that different GII genotypes can cause different severity of clinical manifestations.

13. In conclusion, it is mentioned: "This study demonstrated that norovirus was responsible for 48.4% of diarrhea cases in the study group". Could the authors clarify about the percentage of 48.4%? 31 out of 94 should be 32.9%. It is also not consistent with the abstract (I mention below).

14. Reference no. 6, what journal that publishes this paper? The authors did not mention this. If this is not published in a peer-reviewed journal, it would be better to change the reference with one I recommended.

15. The abstract: "This cross-sectional study involved 31 participants" --> please delete "31". When you design the study, you never know how many patients will participate.
"In total, 91 stool samples were obtained, of which 31 (19%) … " --> please clarify the percentage. Also, is it 91 or 94? Please thoroughly check all the numbers and percentages you mentioned in this paper.

16. Table 2, change "Malutrition" to "Malnutrition". Also, please describe in the methods what the criteria to categorize this nutrition status are.

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Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Virology, infectious diseases, immunology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 31 Jan 2020

Katsumi Shigemura, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Japan

RESPONSES

We greatly appreciate your complimentary comments and suggestions.

1. We apologize that our sample size is too small, however, from this limited sample still we could explore many things.

2. We apologize that electron microscopy is not a method could be used for genotyping. We will revise the manuscript to: Genogroup diversity can be checked using immunochromatography and reverse transcriptase polymerase chain reaction (RT-PCR).

3. We will check the suggested reference and revise our manuscript accordingly.

4. We will revise the manuscript accordingly.

5. We exclude neonates below 1 month old because of our limitation to involve neonates admitted in the neonatal wing to follow the study.

6. Figure 2B lane 1 is considered positive.

7. It is our limitation that we do not include positive controls for each PCR reaction.

8. We will revise the manuscript accordingly.

9. We involve 94 subjects in this study and 31 subjects (32.9%) were norovirus positive.

10. We will check the suggested reference and revise our manuscript accordingly. Our study result showed higher norovirus infection incidence than previous studies mentioning incidence about 17-21% (Oyofo *et al.*, 2002; Subekti *et al.*, 2002; Nirwati *et al.*, 2019). One of the possible contributing factors is because we do not use positive controls for our PCR.

11. We will revise our manuscript accordingly. Norovirus infection is most prevalent in 6-23 months due to protection from maternal antibodies during breastfeeding for infant < 6 months old. After 2 years of age, cases of norovirus will decline due to acquired immunity (Japhet *et al.*, 2012; Trang *et al.*, 2012; El Qazoui *et al.*, 2014; Mikounou Louya *et al.*, 2019).

12. Previous studies have shown different severity in the clinical manifestation of Norovirus GII. Genogroup of Norovirus GII.4, GII.2, GII.3, GII.6, and GII.7 are associated with higher severity score (Mathew *et al.*, 2019). However, it is also difficult to determine whether genogroups or viral loads that associated with clinical severity (Chan *et al.*, 2015)

13 We involve 94 subjects in this study and 31 subjects (32.9%) were norovirus positive. We will revise our manuscript.

14. We will check the suggested reference and revise our manuscript accordingly.

15. We will revise our manuscript accordingly.

16. We will revise our manuscript accordingly. Nutrition status is based on WHO curve for children aged 1-60 months.

We will check the suggested reference and revise our manuscript accordingly. Thank you very much for reviewing our manuscript.

Reference

Chan, M. C. W. *et al.* (2015) 'Virus Genotype Distribution and Virus Burden in Children and Adults Hospitalized for Norovirus Gastroenteritis, 2012-2014, Hong Kong.', *Scientific reports*, 5, p. 11507. doi: 10.1038/srep11507.
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Competing Interests: We have no conflict of interest to declare.

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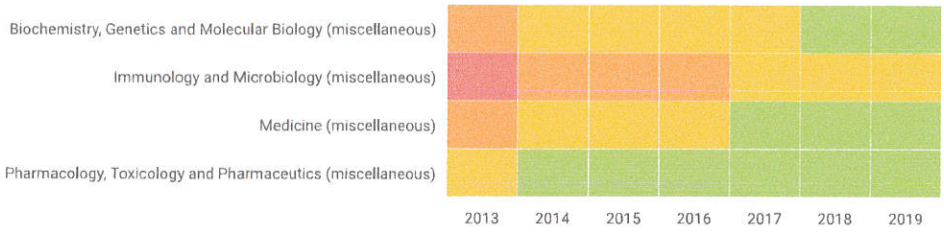

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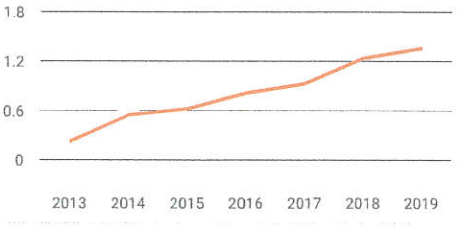

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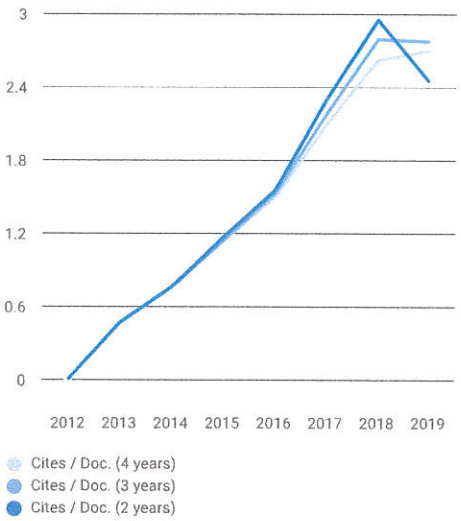

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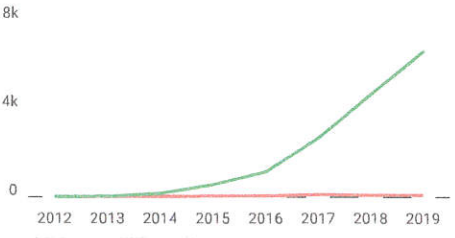

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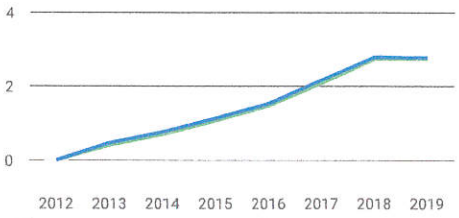

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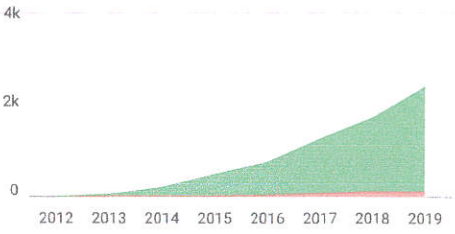

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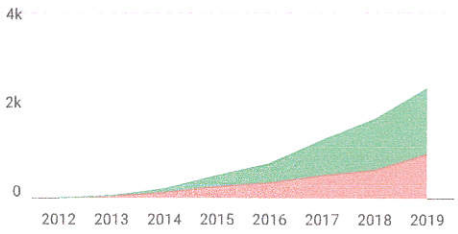

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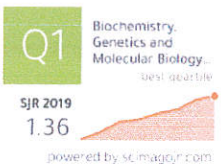

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