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ABOUT COVER

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AIMS AND SCOPE

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ORIGINAL ARTICLE

Retrospective Study

Clinical factors predicting rotavirus diarrhea in children: A cross-sectional study from two hospitals

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Abstract

BACKGROUND
Rotavirus is still a significant contributing morbidity and mortality in pediatric patients.

AIM
To look at clinical signs and symptoms and laboratory findings that can predict rotavirus gastroenteritis compared to non-rotavirus gastroenteritis.

METHODS
This was a cross-sectional study with medical records obtained from December 2015 to December 2019. Inclusion criteria for this study include all hospitalised pediatric patients (0-18 years old) diagnosed with suspected rotavirus diarrhea. The receiver operating curve and Hosmer-Lemeshow test would be used to assess the final prediction findings' calibration (goodness of fit) and discrimination performance.

RESULTS
This study included 267 participants with 187 (70%) rotavirus-diarrhea cases. The patients were primarily male in both rotavirus (65.2%) and non-rotavirus (62.5%) groups. The median age is 1.33 years old (0.08-17.67 years old). Multivariate analysis shows that wet season (OR_{adj} = 2.5; 95%CI: 1.3-4.8, P_{adj} = 0.006), length of stay (LOS) ≥ 3 days (OR_{adj} = 5.1; 95%CI: 1.4-4.8, P_{adj} = 0.015), presence of abdominal pain (OR_{adj} = 3.0; 95%CI: 1.3-6.8, P_{adj} = 0.007), severe dehydration (OR_{adj} = 2.9; 95%CI: 1.1-7.9, P_{adj} = 0.034), abnormal white blood cell counts (OR_{adj} = 2.8; 95%CI: 1.3-6.0, P_{adj} = 0.006), abnormal random blood glucose (OR_{adj} = 2.3; 95%CI: 1.2-4.4, P_{adj} = 0.018) and presence of fecal leukocytes (OR_{adj} = 4.1, 95%CI: 1.7-9.5, P_{adj} = 0.001) are predictors of rotavirus diarrhea. The area under the curve for this model

is 0.819 (95%CI: 0.746-0.878, *P* value < 0.001), which shows that this model has good discrimination.

CONCLUSION
Wet season, LOS ≥ 3 d, presence of abdominal pain, severe dehydration, abnormal white blood cell counts, abnormal random blood glucose, and presence of fecal leukocytes predict rotavirus diarrhea.

Key Words: Rotavirus; Pediatric; Gastroenteritis; Diarrhea; Indonesia

Core Tip: Rotavirus gastroenteritis accounted for 19.11% of diarrheal deaths worldwide in 2019 and is still a leading cause of morbidity and mortality, especially in children under five. This cross-sectional study involving 267 children found that wet season (OR_{adj} = 2.5; 95%CI: 1.3-4.8, P_{adj} = 0.006), length of stay ≥ 3 d (OR_{adj} = 5.1; 95%CI: 1.4-4.8, P_{adj} = 0.015), presence of abdominal pain (OR_{adj} = 3.0; 95%CI: 1.3-6.8, P_{adj} = 0.007), severe dehydration (OR_{adj} = 2.9; 95%CI: 1.1-7.9, P_{adj} = 0.034), abnormal white blood cell counts (OR_{adj} = 2.8; 95%CI: 1.3-6.0, P_{adj} = 0.006), abnormal random blood glucose (OR_{adj} = 2.3; 95%CI: 1.2-4.4, P_{adj} = 0.018) and presence of fecal leukocytes (OR_{adj} = 4.1, 95%CI: 1.7-9.5, P_{adj} = 0.001) are predictors of rotavirus diarrhea.

INTRODUCTION

Rotavirus gastroenteritis accounted for 19.11% of diarrheal deaths worldwide in 2019 and is still a leading cause of morbidity and mortality, especially in children under five. Surveillance data from 2008-2018 showed that 40.78% of all diarrheal diseases in children in Southeast Asia were attributable to rotavirus infection[1]. The fecal-oral transmission from person-to-person contact or ingestion of fecally contaminated food and water commonly leads to a rapid spread among communities, especially in developing countries[2].

When diagnosing gastroenteritis, it is necessary to analyse fecal specimens using widely available assays because rotavirus-caused gastroenteritis cannot be clinically distinguished from that caused by other enteric pathogens[3]. However, because the findings do not change clinical management, which primarily depends on effective rehydration therapy, rotavirus is not routinely tested for in patients with gastroenteritis[4]. Despite its worldwide prevalence, detecting rotavirus in stool samples is still a logistical and financial challenge in developing countries[5].

Considering the disease burden, it is essential to know reliable clinical signs and symptoms and other non-confirmatory laboratory tests that clinicians can use to guide their treatment. Hence, this study aims to look at clinical signs and symptoms and laboratory findings that can predict rotavirus gastroenteritis compared to non-rotavirus gastroenteritis.

MATERIALS AND METHODS

This study was cross-sectional, with medical records obtained from December 2015 to December 2019 from Siloam General Hospital and Siloam Hospital Lippo Village (SHLV). Patients covered by Indonesia's national health insurance can receive care at Siloam General Hospital, a teaching hospital. SHLV, on the other hand, primarily consists of patients who are self-paying or have private insurance. Inclusion criteria for this study include all hospitalised pediatric patients (0-18 years old) diagnosed with suspected rotavirus diarrhea, defined as the passing of ≥ 3 watery or loose stools each day [6]. Children who have previously experienced significant immunosuppression due to prolonged steroid usage or illnesses like the human immunodeficiency virus or primary immunodeficiency were excluded from this study. Another exclusion criterion was the presence of concurrent infections such as urinary tract infections or pneumonia. The sample size calculation used the following formula:

$$N = \frac{z^2(pq)}{e^2} \quad (1)$$

Where N is the sample size, z denotes the standard error, which was 1.96, p was the estimated prevalence in the population, q was 100-p, and e was the acceptable sample error set at 6% in this study. The prevalence of pediatric rotavirus diarrhea in Indonesia is 37.5% to 53.5%[7]. Hence, the minimum sample size required was 265 children.

We collected demographic data such as age, gender, and nutritional status. Clinical signs such as temperature upon arrival, vital signs, clinical manifestations (abdominal pain, respiratory symptoms, dehydration status according to World Health Organization (WHO)[6], duration and frequency of symptoms (diarrhea, vomiting, fever), length of stay (LOS),

treatment given during hospitalisation [intravenous (IV) rehydration and any antibiotics], rotavirus vaccination status, as well as the seasons during which the children contracted diarrhea. The need for IV rehydration represented severe dehydration in this study. Meteorology Climatology and Geophysics Council's data in 2017 were used to determine the seasons where October – February was the rainy season, and the rest was the dry season in Tangerang[8]. We adhered to WHO 2006 growth chart for children below five years, while the Centers for Disease Control and Prevention 2000 growth charts were used for children aged 5-18 years old to classify nutritional status[9]. We did not collect any data on zinc used for diarrhea as all children were given zinc for diarrhea as per standard protocol in our hospitals. Lastly, we collected laboratory findings such as complete blood count, serum electrolytes, random blood glucose, erythrocyte sedimentation rate (ESR), and urinary ketone for dehydration markers and fecal leukocytes[10]. We present laboratory values dichotomously (normal *vs* abnormal values) for multivariate analysis and in numerical forms for descriptive purposes. The reference range will be based on our population study's mean or median age group.

The neutrophil-lymphocyte ratio (NLR) is obtained by dividing the total band and segmented neutrophil by the lymphocyte. In contrast, the monocyte-lymphocyte ratio is obtained by dividing the monocyte by the lymphocyte. Absolute neutrophil count is calculated with the formula as follows: (Total WBC × % [PMNs + bands]) ÷ 100.

While the absolute lymphocyte count is calculated with the formula: WBC count × 1000 × % lymphocyte. (NLR were obtained by dividing the total neutrophils by lymphocyte counts, and the same methodology was applied to obtain lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR)[11]. One or two ccs of peripheral venous blood samples were collected by antecubital venipuncture into vacutainer tubes (Becton Dickinson, Rutherford, NJ, United States) containing tri potassium ethylenediaminetetraacetic acid. The complete blood count was done within one to two hours after the blood samples were drawn, and the analysis was performed using the Advia 2120i automated analyser (Siemens Healthcare Diagnostics, Deerfield, IL, United States). Erythrocyte sedimentation rate levels were measured by TEST 1 (Alifax, Padova, Italy). The rotavirus analysis was done using immunochromatography (Alcore One-Step Rotavirust Test). Those who tested positive would be categorised as having rotavirus diarrhea, and those who tested negative would be categorised as having non-rotavirus diarrhea. Strict quality control procedures were adopted. All of the independent variables were chosen based on previous studies[7,12,13].

The data was processed using IBM SPSS 26.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, United States). After a normality test, data with a normal distribution will be presented as mean and standard deviation. If not, the median and range will be applied. The Mann-Whitney-U test is used when the distribution of numerical data is non-normal, while the T-test is used when the distribution of numerical data is normal. Chi-square was used for bivariate analysis, and variables with p-values less than 0.25 would be used in multivariate logistic regression analysis. The receiver operating curve (ROC) and Hosmer-Lemeshow test would be used to assess the final prediction findings' calibration (goodness of fit) and discrimination performance. The area under the curve (AUC) is equal to 0.5 when the ROC curve represents chance, and it is equal to 1.0 when the ROC curve represents accuracy. A good calibration would be indicated by a *P* value > 0.05. The sensitivity and specificity of the various predictor variables in identifying non-severe and severe pneumonia were then calculated using the area under the curve. We also analysed casewise diagnostics to identify any outliers.

This study protocol was approved by the Committee on Ethics at the University of Pelita Harapan, Tangerang, Indonesia, with Code Ethic No. 430/FK-UPH/Ext./V/2019. The ethical board exempted informed consent due to the retrospective nature of our study. Identities were removed entirely, and data were analysed anonymously.

RESULTS

Descriptive characteristics

This study included 267 participants with 187 (70%) rotavirus-diarrhea cases (Table 1). The patients were primarily male in both rotavirus (65.2%) and non-rotavirus (62.5%) groups. The median age is 1.33 years old (0.08-17.67 years old), with the majority belonging to the 0-11 mo old category (34.5%). Most patients had good nutritional status in the non-rotavirus group (51.3%) and rotavirus group (53.5%). Most rotavirus cases occurred during the dry season (77.1%), while non-rotavirus cases occurred mainly in the wet seasons (37.8%) with an odds ratio (OR) of 0.49 [95% confidence interval (CI) 0.29-0.93, *P* value 0.01]. The majority of patients had a length of stay of ≥ 3 d in both groups (95% in the non-rotavirus group and 83.4% in the rotavirus group) (OR 0.27; 95%CI: 0.1-0.78, *P* value 0.02). Only one patient was put in the intensive care unit, belonging to the non-rotavirus group. In both groups, most patients are not vaccinated for rotavirus (86.3% in non-rotavirus diarrhea *vs* 94.7% in rotavirus diarrhea) with an OR of 0.35 (95%CI: 0.14-0.97, *P* value 0.04) (Table 1).

Clinical manifestations

The clinical manifestations vary between the two groups. Most patients presented with mild-moderate dehydration (67.4%) in rotavirus diarrhea, while most in the non-rotavirus group presented with no dehydration (43.8%). Fever mostly lasts less than three days for rotavirus diarrhea (55.1%), while fever lasts mostly ≥ 3 d in the non-rotavirus group (56.3%). The last difference in clinical manifestation between the two groups is in diarrhea duration, where in rotavirus diarrhea it lasts 2-4 d (51.3%) while it mostly lasts > 4 d (57.5%) in the non-diarrhea group. Meanwhile, in both groups, most patients suffer from more than five diarrhea episodes per day, 0-3 vomiting episodes, abdominal pain, and respiratory symptoms (Figure 1).

Table 1 Characteristics of the study population

Characteristics	Frequency		OR (95%CI)	P value
	Non-rotavirus	Rotavirus		
Gender				
Male	50 (29.1)	122 (70.9)	0.89 (0.52-1.53)	0.77
Female	30 (31.6)	65 (68.4)		
Age (mo)				
0-11	21	71	Ref	Ref
12-23	24	60	0.74 (0.38-1.46)	0.38
24-59	17	44	0.77 (0.37-1.61)	0.48
≥ 60	18	12	0.19 (0.08-0.47)	< 0.001
Nutritional status				
Severely underweight	10	34	1.39 (0.63-3.08)	0.4
Underweight	14	32	0.94 (0.45-1.94)	0.86
Normoweight	41	100	Ref	Ref
Overweight	7	6	0.35 (0.11-1.11)	0.08
Obese	8	15	0.77 (0.30-1.95)	0.58
Season				
Dry	32 (22.9)	108 (77.1)	0.49 (0.29-0.83)	0.01
Wet	48 (37.8)	79 (62.2)		
Hospitalisation				
In-patient	79 (29.7)	187 (70.3)	N/A	0.30
Intensive Care Unit	1 (100)	0 (0)		
Length of stay (d)				
< 3	4 (11.4)	31 (88.6)	0.27 (0.10-0.78)	0.02
≥ 3	76 (32.8)	156 (67.2)		
Clinical manifestations				
Diarrhea duration (d)				
< 2	2 (22.2)	7 (77.8)	Ref	Ref
2-4	32 (25)	96 (75)	0.86 (0.17-4.34)	1
> 4	46 (35.4)	84 (64.6)	0.52 (0.10-2.62)	0.72
Diarrhea frequency (d)				
< 3	4 (66.7)	2 (33.3)	Ref	Ref
3-4	32 (30.2)	74 (69.8)	4.63 (0.81-26.54)	0.08
> 5	44 (28.4)	111 (71.6)	5.05 (0.90-28.54)	0.07
Vomiting frequency (d)				
0-3	50 (36)	89 (64)	Ref	Ref
4-5	9 (20)	36 (80)	2.25 (1.00-5.04)	0.07
> 5	21 (25.3)	62 (74.7)	1.66 (0.91-3.04)	0.13
Fever duration (d)				
< 3	35 (25.4)	103 (74.6)	0.63 (0.38-1.01)	0.12
≥3	45 (34.9)	84 (65.1)		
Abdominal pain				

Negative	56 (25)	168 (75)	0.26 (0.14-0.52)	< 0.01
Positive	24 (55.8)	19 (44.2)		
Respiratory symptoms				
Negative	59 (28.8)	146 (71.2)	0.79 (0.43-1.45)	0.54
Positive	21 (33.9)	41 (66.1)		
Dehydration				
No dehydration	35 (46.7)	40 (53.3)	Ref	Ref
Mild-moderate	33 (20.8)	126 (79.2)	3.34 (1.85-6.10)	< 0.01
Severe	12 (36.4)	21 (63.6)	1.53 (0.66-3.55)	0.43
Treatment				
Antibiotic				
Negative	3 (1.7)	176 (98.3)	0.002 (0.001-0.01)	< 0.01
Positive	77 (87.5)	11 (12.5)		
IV rehydration				
Negative	19 (32.2)	40 (67.8)	1.15 (0.61-2.13)	0.80
Positive	61 (29.3)	147 (70.7)		
Rotavirus vaccination				
Negative	69 (28)	177 (72)	0.35 (0.14-0.97)	0.04
Positive	11 (52.4)	10 (47.6)		
Laboratory examinations				
Hemoglobin				
Normal	52 (28.1)	133 (71.9)	0.75 (0.43-1.32)	0.40
Abnormal	28 (34.1)	54 (65.9)		
White blood cell count				
Normal	50 (24.6)	153 (75.4)	0.37 (0.21-0.67)	< 0.01
Abnormal	30 (46.9)	34 (53.1)		
Basophils				
Normal	63 (31.5)	137 (68.5)	1.35 (0.72-2.53)	0.43
Abnormal	17 (25.4)	50 (74.6)		
Eosinophils				
Normal	23 (26.1)	65 (73.9)	0.76 (0.43-1.34)	0.42
Abnormal	57 (31.8)	122 (68.2)		
Band neutrophils				
Normal	66 (30.7)	149 (69.3)	1.20 (0.61-2.37)	0.72
Abnormal	14 (26.9)	38 (73.1)		
Segment neutrophils				
Normal	9 (18.8)	39 (81.3)	0.48 (0.22-1.05)	0.09
Abnormal	71 (32.4)	148 (67.6)		
Total neutrophils				
Normal	10 (20.4)	39 (79.6)	0.54 (0.26-1.15)	0.15
Abnormal	70 (32.1)	148 (67.9)		
Lymphocytes				
Normal	13 (26)	37 (74)	0.79 (0.40-1.58)	0.61

Abnormal	67 (30.9)	150 (69.1)		
Monocytes				
Normal	44 (32.1)	93 (67.9)	1.24 (0.73-2.10)	0.51
Abnormal	36 (27.7)	94 (72.3)		
Absolute lymphocytes count				
Normal	28 (23.5)	91 (76.5)	0.57 (0.33-0.98)	0.05
Abnormal	52 (35.1)	96 (64.9)		
Absolute neutrophils count				
Normal	40 (23.8)	128 (76.2)	0.46 (0.30-0.79)	0.007
Abnormal	40 (40.4)	59 (59.6)		
Neutrophils-to-lymphocyte ratio				
Normal	33 (29.5)	4 (57.1)	0.96 (0.57-1.63)	0.99
Abnormal	77 (29.6)	183 (70.4)		
Lymphocyte-to-monocyte ratio				
Normal	3 (42.9)	4 (57.1)	1.79 (0.40-8.15)	0.74
Abnormal	77 (29.6)	183 (70.4)		
Platelet-to-lymphocyte ratio				
Normal	6 (22.2)	21 (77.8)	0.64 (0.25-1.64)	0.47
Abnormal	74 (31)	165 (69)		
Erythrocyte sedimentation rate				
Normal	37 (31.1)	82 (68.9)	1.1 (0.65-1.86)	0.82
Abnormal	43 (29.1)	105 (70.9)		
Random blood glucose				
Normal	45 (24.6)	138 (75.4)	0.46 (0.26-0.80)	0.007
Abnormal	35 (41.7)	49 (58.3)		
Sodium				
Normal	42 (27.5)	111 (72.5)	0.76 (0.45-1.28)	0.37
Abnormal	38 (33.3)	76 (66.7)		
Potassium				
Normal	33 (29.5)	79 (70.5)	0.96 (0.56-1.63)	0.99
Abnormal	47 (30.3)	108 (69.7)		
Chloride				
Normal	42 (29.6)	100 (70.4)	0.96 (0.57-1.63)	0.99
Abnormal	38 (30.4)	87 (69.6)		
Urine and fecal tests				
Urinary ketone				
Negative	74 (29.8)	174 (70.2)	0.92 (0.34-2.52)	1.00
Positive	6 (31.6)	13 (68.4)		
Fecal leukocytes				
Negative	58 (25.9)	166 (74.1)	0.33 (0.17-0.65)	0.002
Positive	22 (51.2)	21 (48.8)		

N/A: Not applicable.

Treatment

98.3% of patients that are rotavirus positive did not receive antibiotics. In comparison, almost all (96.3%) patients who suffer from non-rotavirus diarrhea receive antibiotics with an OR of 0.002 (95%CI: 0.001-0.01, *P* value < 0.01). In both groups, most patients receive IV rehydration with no significant statistical difference (OR 1.15; 95%CI: 0.61-2.13, *P* value 0.08).

Laboratory parameters

Most laboratory parameters are within normal range except for decreased LMR and PLR in both groups, while ESR is slightly elevated. The potassium level is also slightly below the normal reference range, with a median of 4 mmol/L in both groups. Most urinary ketones are negative in both groups (92.5% in the non-rotavirus *vs* 93% in the rotavirus group). There is a significant difference in fecal leukocyte findings between both groups with an OR of 0.33 (95%CI: 0.17-0.65, *P* value 0.002) (Tables 1 and 2).

Multivariate logistic regression

Multivariate logistic regression analysis adjusted for variables with a p-value of < 0.25 is shown in Table 3. Multivariate analysis shows that wet season (OR_{adj} = 2.5; 95%CI: 1.3-4.8, P_{adj} = 0.006), LOS ≥ 3 d (OR_{adj} = 5.1; 95%CI: 1.4-4.8, P_{adj} = 0.015), presence of abdominal pain (OR_{adj} = 3.0; 95%CI: 1.3-6.8, P_{adj} = 0.007), severe dehydration (OR_{adj} = 2.9; 95%CI: 1.1-7.9, P_{adj} = 0.034), abnormal white blood cell counts (OR_{adj} = 2.8; 95%CI: 1.3-6.0, P_{adj} = 0.006), abnormal random blood glucose (OR_{adj} = 2.3; 95%CI: 1.2-4.4, P_{adj} = 0.018) and presence of fecal leukocytes (OR_{adj} = 4.1, 95%CI: 1.7-9.5, P_{adj} = 0.001) are predictors of rotavirus diarrhea. The Hosmer-Lemeshow test shows this model is a good fit with a p-value of 0.361. The AUC for this model is 0.819 (95%CI: = 0.746-0.878, *P* value < 0.001), which shows that this model has good discrimination (Figure 1).

DISCUSSION

Comparison with other studies

Rotavirus was shown to be the leading cause of morbidity and mortality in children, especially five years old and below [13]. Symptoms tend to be most severe in children between 3-24 mo old. However, in approximately 25% of rotavirus cases, severe disease occurs after two years of age. Serologic evidence of rotavirus infection can be virtually observed in all children aged 4-5[12]. Our results showed that our samples have a median age of 1.3 years old. In multivariate analysis, the wet season showed a significant association with rotavirus infection. A previous study showed that in the tropics, rotavirus infection tends to occur all year round compared to the seasonal pattern of infection in countries with temperate climates. However, factors other than temperature, such as rainfall and humidity, play a significant role in rotavirus incidence in the tropics. Due to the waterborne nature of rotavirus transmission, the outbreak pattern might be altered by precipitation levels[14]. In low-income areas, stagnant water sources and poor access to uncontaminated water and sanitation were hypothesised to pose a higher risk for rotavirus infection[15]. Study showed that monsoon season was significantly correlated with dehydrating rotavirus diarrhea among children aged 0-59 mo in South Asia[16]. Previous meta-analyses have also concluded that every 1'C increase in temperature is associated with a 4%-10% decrease in rotavirus infection incidence in the tropics. However, for every one-centimetre increase in mean monthly rainfall and 1% increase in relative humidity (22%), rotavirus incidence decreased by 1% and 3%, respectively. Based on the evidence, it was previously concluded that rotavirus incidence in the tropics was the highest during colder and drier times of the year[17].

Gastroenteritis is generally more severe in the rotavirus group than in the non-rotavirus sample. Length of stay was shown to be prolonged in children age below two years old with rotavirus gastroenteritis. Prolonged LOS, especially in pediatric patients, promote work absenteeism in 70% of parents and could negatively impact the quality of life[18]. Prolonged LOS ≥ 3 d is significantly associated with rotavirus gastroenteritis in this study.

Rotavirus has a broad spectrum of symptoms after 1 to 3 d of incubation, varying from subclinical illness to severe dehydration, shock and death. Rotavirus infection has a similar but more severe clinical manifestation than other gastrointestinal infections. Diagnosis of rotavirus gastroenteritis is commonly clinical based on the presence of vomiting and low-grade fever, followed by watery, non-bloody diarrhea. Moderate fever (temperature < 39°C) is found in approximately one-third of infected patients. Fever and vomiting frequently cease within 1 to 3 d. This finding explains our findings that prolonged fever and vomiting are not significantly associated with rotavirus gastroenteritis. Other physical findings such as abdominal cramping, fatigue and signs of dehydration might also occur during the 5 to 7 d disease course. Diagnosis can be further established by the absence of atypical features such as high-grade fever, which is more commonly present in bacterial gastroenteritis, projectile vomiting, bilious vomiting, blood or mucus in stool, persistent diarrhea for more than seven days, focal abdominal pain, absent bowel sound, and history of antibiotic use[4,19,20]. Presence of abdominal pain and severe dehydration was associated with rotavirus infection in this study. These findings correlate with findings from the previous study that rotavirus-positive subjects were more likely to present with severe dehydration and tend to require intravenous rehydration therapy than rotavirus-negative subjects[16]. However, the role of abdominal pain as a predictor of rotavirus infection is still controversial. Abdominal pain is hypothesised to be limited in rotavirus infection due to low inflammatory response demonstrated by minimal elevation of C-reactive protein or calprotectin levels as clinical markers of inflammation. Rotavirus replication appears to be limited exclusively in the villous epithelium of small intestines, and the diarrhea was considered malabsorptive secondary to enterocyte destruction. Despite non-specific symptomatology, severe abdominal pain and tenesmus tend to indicate large intestines

Table 2 Descriptive values of the laboratory findings

Variable	Reference range	Non rotavirus	Rotavirus
Hemoglobin (g/dL)	10.5-14.0	13.49 (± 16.0)	13.0 (± 11.3)
White blood cell count (10^9 L)	6.0-17.5	14.54 (4.21-42.07)	11.72 (2.86-38.6)
Basophils (%)	0-0.75	0 (0-1)	0 (0-1)
Eosinophils (%)	1-3	0 (0-5)	0 (0-5)
Band neutrophils (%)	3-5	3 (2-12)	3 (1-8)
Segment neutrophils (%)	54-62	62 (20-90)	51 (15-92)
Total neutrophils (%)	58-66	65 (23-93)	54 (18-95)
Lymphocytes (%)	25-33	27 (3-69)	37 (3-75)
Monocytes (%)	3-7	7 (3-13)	7 (1-15)
Absolute lymphocyte count	4000-10500	3354.6 (290.1-15356)	4232.8 (459-24532.2)
Absolute neutrophils count	1500-8500	8662 (1768.7-32814.6)	6100 (972.4-27898)
Neutrophil-to-lymphocyte ratio	Male: 1.48-6.37; Female: 1.22-5.59	2.5 (0-31)	2 (0-32)
Lymphocyte-to-monocyte ratio	Male: 11.12-26.82; Female: 16.08-28.18	4.29 (0.38-16.50)	5.29 (0.50-54)
Platelet-to-lymphocyte ratio	Male: 132.07-178.53; Female: 132.46-181.90	96.7 (20.5-722)	98 (15.89-969)
Thrombocyte count (μ/mm^3)	150000-350000	350000 (109800-1099000)	381000 (115000-1094000)
Erythrocyte sedimentation rate (mm/hour)	0-10	12 (2-215)	14 (1-68)
Random blood glucose (mg/dL)	60-100	94.5 (48-238)	85 (15-160)
Sodium (mmol/L)	134-143	136 (113-154)	135 (124-165)
Potassium (mmol/L)	4.1-5.3	4 (1.6-5.9)	4 (1.4-7.1)
Chloride (mmol/L)	98-106	100 (34.5-134)	101 (9.7-141)

Table 3 Results from multivariate logistic regression analysis for rotavirus diarrhea

Values	OR$_{adj}$ (95%CI)	*P* value$_{adj}$
Wet season	2.5 (1.3-4.8)	0.006
Length of stay ≥ 3 d	5.1 (1.4-4.8)	0.015
Fever lasts ≥ 3 d	1.9 (0.97-3.5)	0.06
Abdominal pain	3.0 (1.3-6.8)	0.007
Mild-moderate dehydration	1.2 (0.4-3.5)	0.75
Severe dehydration	2.9 (1.1-7.9)	0.034
Abnormal white blood cell counts	2.8 (1.3-6.0)	0.006
Abnormal absolute neutrophil counts	1.9 (0.9-3.8)	0.072
Abnormal random blood glucose	2.3 (1.2-4.4)	0.018
Presence of fecal leukocytes	4.1 (1.7-9.5)	0.001

CI: Confidence intervals; OR: Odds ratio, OR$_{adj}$: Adjusted odds ratio.

involvement[21,22]. Previous studies demonstrated that abdominal pain is particularly frequent in rotavirus-positive subjects or co-infection with rotavirus subjects. However, no significant association has been found in statistical analyses [23]. Ambiguous interpretation of abdominal pain by parents of young children during history taking could lead to a bias in pain assessment. This finding might explain the contradictory result regarding abdominal pain in this study.

Rotavirus diarrhea and laboratory values
In this study, rotavirus-positive patients demonstrated abnormal white blood cell counts and abnormal random blood glucose. However, previous studies showed no significant difference in white blood cell count between the rotavirus-
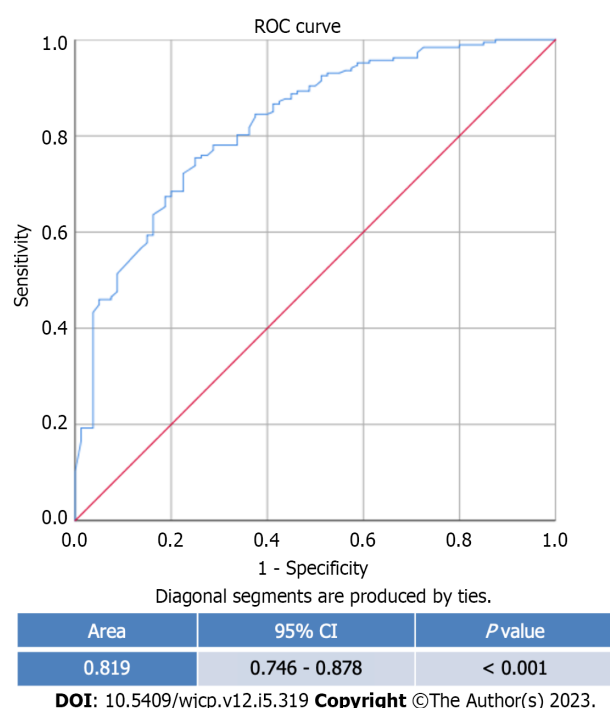
Area	95% CI	*P* value
0.819	0.746 - 0.878	< 0.001

Figure 1 The receiver operating curve curve analysis.

positive and rotavirus-negative groups. These studies did not mainly compare rotavirus and the specific etiologic agent of gastroenteritis[24-26]. The wide causative range of non-rotavirus gastroenteritis might explain the different findings. Other more significant variables to be compared with rotavirus are indicators of metabolic acidosis secondary to fluid loss. A previous study showed that rotavirus-positive subjects had lower blood pH, higher base deficit, and lower bicarbonate[25]. Complete blood count examination appears to have minimal value in predicting rotavirus infection.

Rotavirus diarrhea and respiratory symptoms

Several reports have stated that respiratory symptoms might also occur during the rotavirus infection course. However, the mechanism that explains this finding is still controversial. Coincidental infection with respiratory viruses during rotavirus endemic season might manifest as respiratory symptoms. Previous studies have indicated that rotavirus might infect extra-intestinal organs during viremia, but there has not been sufficient evidence to prove its replication ability outside the intestine. Rotavirus antigens or RNA were detected in the spleen, heart, kidneys, testes, bladder, liver, cells or secretions from the respiratory tract, and endothelial cells[20,27]. Our result showed that respiratory symptoms do not predict rotavirus infection in children. Stool analyses in rotavirus-positive subjects are common without blood or white blood cells[20]. This result correlates with our findings that faecal leukocytes are a predictor of rotavirus infection. The presence of fecal leucocytes in rotavirus infection may indicate inflammatory processes in the intestines[28]. No other hematologic findings were significantly correlated with rotavirus infection in this study.

Limitation

This study has its limitations. Our research is a cross-sectional study to start with. As a result, we could not account for some factors that might affect the severity of rotavirus diarrhea, such as birth weight, source of water, and house-crowding status. Second, the study's focus on just two institutions raises the possibility that this study may not be generalisable to other centres. However, given the nature of the two different hospitals, we were able to include kids from a range of racial and ethnic backgrounds, assuring that both high- and low-income parents were represented in this study. Some variables have insufficient strength for analysis due to missing or unanalysed laboratory data. Third, we could not account for any temporal changes occurring in the four years of the study period. Any seasonality, changes in guidelines and diagnosis of rotavirus diarrhea, as well as immunization update may have altered the results of the study. Lastly, we did not analyse the antigenic properties of the rotavirus due to limited equipment and funding.

CONCLUSION

In this study, wet season, LOS ≥ 3 d, presence of abdominal pain, severe dehydration, abnormal white blood cell counts, abnormal random blood glucose and presence of fecal leukocytes predict rotavirus diarrhea. Since these parameters have good discrimination, these findings should alert clinicians to the presence of rotavirus diarrhea. Clinicians may use these parameters to further alert them to the possibility of rotavirus diarrhea in children and order tests more prudently as well as prescribing appropriate therapy.

Research background

Rotavirus gastroenteritis accounted for 19.11% of diarrheal deaths worldwide in 2019 and is still a leading cause of morbidity and mortality, especially in children under five. Surveillance data from 2008-2018 showed that 40.78% of all diarrheal diseases in children in Southeast Asia were attributable to rotavirus infection.

Research motivation

Rotavirus diarrhea is still a leading cause of mortality among Indonesian children. However, since antigen detection is not affordable amongst many families, other cheap clinical proxies for rotavirus diarrhea must be determined.

Research objectives

This study aims to determine clinical and laboratory values that may serve as an indicator to raise clinicians' awareness about rotavirus diarrhea.

Research methods

This study was cross-sectional, with medical records obtained from December 2015 to December 2019 from Siloam General Hospital and Siloam Hospital Lippo Village. Inclusion criteria for this study include all hospitalised pediatric patients (0-18 years old) diagnosed with suspected rotavirus diarrhea, defined as the passing of ≥ 3 watery or loose stools each day. We collected demographic data such as age, gender, and nutritional status. Clinical signs such as temperature upon arrival, vital signs, clinical manifestations (abdominal pain, respiratory symptoms, dehydration status according to World Health Organization), duration and frequency of symptoms (diarrhea, vomiting, fever), length of stay (LOS), treatment given during hospitalisation [intravenous (IV) rehydration and any antibiotics], rotavirus vaccination status, as well as the seasons during which the children contracted diarrhea.

Research results

This study included 267 participants with 187 (70%) rotavirus-diarrhea cases. The patients were primarily male in both rotavirus (65.2%) and non-rotavirus (62.5%) groups. The median age is 1.33 years old (0.08-17.67 years old). Multivariate analysis shows that wet season (OR_{adj} = 2.5; 95%CI: 1.3-4.8, P_{adj} = 0.006), LOS ≥ 3 d (OR_{adj} = 5.1; 95%CI: 1.4-4.8, P_{adj} = 0.015), presence of abdominal pain (OR_{adj} = 3.0; 95%CI: 1.3-6.8, P_{adj} = 0.007), severe dehydration (OR_{adj} = 2.9; 95%CI: 1.1-7.9, P_{adj} = 0.034), abnormal white blood cell counts (OR_{adj} = 2.8; 95%CI: 1.3-6.0, P_{adj} = 0.006), abnormal random blood glucose (OR_{adj} = 2.3; 95%CI: 1.2-4.4, P_{adj} = 0.018) and presence of fecal leukocytes (OR_{adj} = 4.1, 95%CI: 1.7-9.5, P_{adj} = 0.001) are predictors of rotavirus diarrhea. The area under the curve for this model is 0.819 (95%CI: = 0.746-0.878, P value < 0.001), which shows that this model has good discrimination.

Research conclusions

In this study, wet season, LOS ≥ 3 d, presence of abdominal pain, severe dehydration, abnormal white blood cell counts, abnormal random blood glucose and presence of fecal leukocytes predict rotavirus diarrhea. Since these parameters have good discrimination, these findings should alert clinicians to the presence of rotavirus diarrhea. Clinicians may use these parameters to further alert them to the possibility of rotavirus diarrhea in children and order tests more prudently as well as prescribing appropriate therapy.

Research perspectives

More bigger and confirmatory studies are needed to confirm our findings.

FOOTNOTES

Country/Territory of origin: Indonesia

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