

Çocukluk Çağı Viral Gastroenteritlerin Hastane Yatışlarında Nötrofil/Lenfosit Oranının Etkinliği

The Effectiveness of Neutrophil/Lymphocyte Ratio in Hospitalization of Childhood Viral Gastroenteritis

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ÖZ

GİRİŞ ve AMAÇ: Akut gastroenterit inflamatuvar bir hastalıktır. İnflamasyon biyobelirteçlerinden biri olan nötrofil/lenfosit oranı (NLO) akut gastroenteritli hastalarda hastalığın ciddiyeti ile uyumlu olabilir. Bu çalışmada dışkıda rota ve/veya adeno virüs antijen pozitifliği olan akut gastroenteritli çocuklarda kanda NLO'nun servis yatışına etkisinin olup olmadığının belirlenmesi amaçlanmıştır.

YÖNTEM ve GEREÇLER: Bu çalışmada Ocak 2018 ile Ocak 2019 tarihleri arasında akut gastroenterit nedeniyle acil servise başvuran ve dışkıda rota ve/veya adeno virüs antijeni pozitifliği saptanan 438 çocuk hasta retrospektif olarak incelendi.

BULGULAR: Çalışmaya dışkıda rota ve/veya adeno virüs antijeni pozitif olan 438 çocuk dahil edildi. NLO ile hastaların hospitalizasyonu arasında da gruplar arasında istatistiksel olarak anlamlı bir fark bulunmaktadır ($p < 0,001$). Yatan hastaların NLO'su $2,60 \pm 3,73$, ayaktan takip edilen hastaların nötrofil lenfosit oranı $4,23 \pm 5,37$.

TARTIŞMA ve SONUÇ: Akut gastroenterit nedeni pediatrik başvurularda; dışkıda adeno ve rotavirüs antijen pozitifliği ile adenovirüs antijen pozitifliği saptanan hastalar arasında NLO oranında, hospitalizasyon açısından istatistiksel olarak anlamlı bir fark saptanmıştır.

Anahtar Kelimeler: Akut gastroenterit, çocuklar, Nötrofil / Lenfosit oranı

ABSTRACT

INTRODUCTION: Acute gastroenteritis is an inflammatory disease. Neutrophil/lymphocyte ratio (NLR), one of the inflammation biomarkers, may be compatible with the severity of the disease in patients with acute gastroenteritis. In this study, we aimed to determine whether NLR in the blood has an effect on hospitalization in children with acute gastroenteritis with rota and / or adenovirus antigen positivity in the stool.

METHODS: Between January 2018 and January 2019, 438 children admitted to the emergency department due to acute gastroenteritis and who were found to have rota and / or adenovirus antigen positivity were examined retrospectively.

RESULTS: 438 children with rota and / or adenovirus antigen positive in their stool were included in the study. There was a statistically significant difference between NLO and hospitalization of patients as well as between groups ($p < 0.001$). NLR of inpatients was 2.60 ± 3.73 and neutrophil lymphocyte ratio of outpatients was 4.23 ± 5.37 .

DISCUSSION AND CONCLUSION: In pediatric admissions due to acute gastroenteritis, there was a statistically significant difference in terms of hospitalization in NLR between the adeno and rotavirus antigen positivity in the stool and adenovirus antigen patients with antigen positivity.

Keywords: Acute gastroenteritis, children, Neutrophil/Lymphocyte ratio.

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INTRODUCTION

Gastroenteritis, which is one of the most common infections in childhood, is one of the leading causes of mortality and morbidity (1). According to the World Health Organization (WHO), diarrhea is defined as the passage of three or more loose or liquid stools per day, or more frequently than normal is.

Diarrhea generally lasts less than 7 days and does not exceed 14 days. All attacks of diarrhea and vomiting that last less than two weeks are regarded as acute gastroenteritis. Diarrhea may be accompanied by fever and / or vomiting (3). Gastroenteritis is an important case because it leads to acute dehydration, malnutrition, developmental disorders, inappropriate drug use and even death (4).

Viruses, bacteria, protozoa, helminths and fungi cause infections of the gastrointestinal tract. Viruses are responsible for the vast majority of gastroenteritis. Rotaviruses are the most common viral agents. Rotaviruses are the leading cause of diarrhea seen in infants and young children worldwide, and especially severe gastroenteritis causing hospitalization and infant mortality (5). Rotavirus is responsible for approximately 40% of hospitalizations due to acute gastroenteritis (6). It is frequently seen among children especially under 2 years old in the winter months (7). Enteric adenoviruses are the second most common group of viruses that require hospitalization after rotaviruses. There are six groups of adenoviruses and enteric adenoviruses belong to the group F. Two serotypes (adenovirus 40 and 41) draw attention in diarrhea cases (2). The disease occurs at the end of the incubation period of 8-10 days and is characterized by liquid stool, which lasts up to 10 days. It affects children under 2 years old, especially in developing countries.

The diagnosis of viral gastroenteritis is performed by electron microscopy or molecular investigations the virus in feces, ELISA test and other immunological tests. Complete blood count

(CBC) is an easy and inexpensive test. Some important parameters such as leukocyte (WBC), neutrophil, lymphocyte, platelet counts and mean platelet volume (MPV) are studied in the test.

CBC parameters may vary significantly in inflammation. An increase especially in neutrophil and platelet count is observed, while lymphocyte count is decreased (8).

NLR is an indicator which is calculated by using neutrophil and lymphocyte values in CBC and its role in pathophysiology has been increasing. It is generally accepted as a simple, fast, easy-to-apply and inexpensive indicator of subclinical inflammation (9).

NLR is calculated from the peripheral blood sample as the ratio of neutrophil count to lymphocyte count. Calculated from CBC, NLR is an easily accessible biomarker and does not require special equipment or analysis. It has been reported that NLR increases in such conditions as ulcerative colitis, pancreatitis, myelofibrosis, and larynx carcinoma (10).

In this study, we aimed to investigate the effect of NLR on hospitalization in CBC in children admitted to our emergency department due to acute gastroenteritis and who had positive adenovirus and rotavirus antigen in their stool.

MATERIAL AND METHODS

This study was conducted with the approval of the local ethics committee number 2019-137. For this study, 9770 children, admitted to our emergency department due to acute gastroenteritis between January 2018 and January 2019, were retrospectively examined. The study included 438 children with positive route and / or adenovirus antigen in their stools. Patients who were diagnosed with acute gastroenteritis in the emergency department but had no rota and adenovirus in the stool, those with incomplete information on the study file and patients over 18 years of age were excluded from the study (Figure 1).

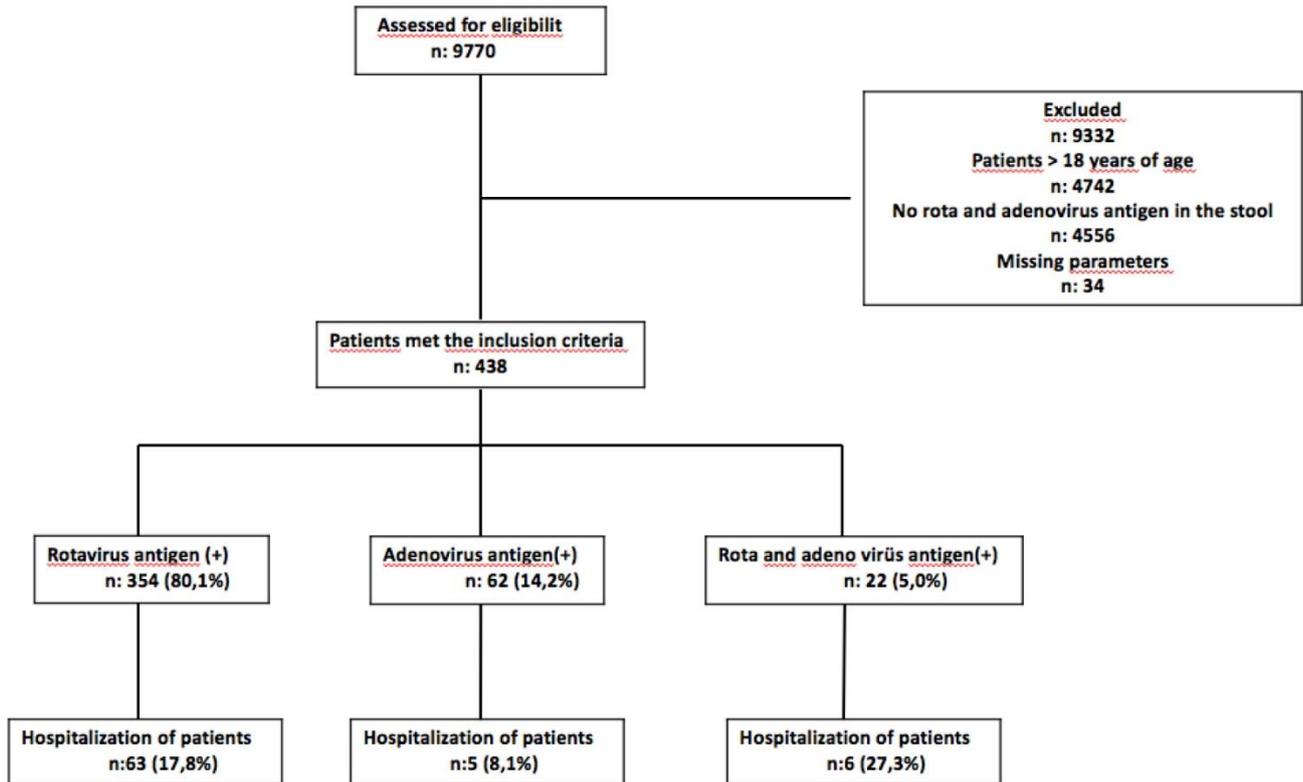


Figure 1: Flow chart of pediatric patients presenting with acute gastroenteritis and with rotavirus and/or adenovirus antigen in stool

From medical records in patient files, age, gender, complaints, physical examination findings, vital signs, laboratory data, CBC parameters (WBC, hemoglobin level, platelet count, MPV, neutrophil, lymphocyte, monocyte and eosinophil numbers) and C-reactive protein (CRP) values and treatment methods were recorded. NLR was obtained by dividing the neutrophil count by the lymphocyte count. Pentra df nexus 1200 device was used in the complete blood count of all patients. Emergency outcomes of the patients were determined as discharge or hospitalization.

In our study, “Ecotest RAC (Rota-ado Card Test) -F23M, PRC” kits, a colour chromatographic test performing qualitative detection of rotavirus and adenovirus in fresh stool samples, were studied in accordance.

Statistical Analysis

Statistical analysis was performed using SPSS version 22 (SPSS, Inc, Chicago, IL) software. The suitability of the data to normal distribution was examined by Kolmogorov-Smirnov / Shapiro-Wilk

test. Descriptive statistics were determined as number and percentage for categorical variables and mean and standard deviation for numerical variables. The average of normally distributed numerical values was compared using the paired t- test and the average of non-normally distributed numerical values was compared using the Mann Whitney U test. $p < 0.05$ was evaluated as statistically significant. The distribution of rotavirus and adenovirus frequency according to seasons and age was evaluated using the chi-square test. $p < 0.05$ was considered statistically significant.

RESULTS

As a preliminary diagnosis, a total of 9770 stool specimens with acute gastroenteritis were evaluated retrospectively and evaluated. The study included 438 children with positive rota and / or adenovirus antigen in stool. The average age was 4.03 ± 3.65 . 203 (46.3%) of 438 patients were female and 235 (53.7%) were male (Table 1).

Table 1: Distribution of children who have positive rotavirus and/or adenovirus antigen in stool, by gender, age and season

	Number of Patients N(%)	Rotavirus N(%)	Adenovirus N(%)	Rota and adenovirus N(%)	P
Gender					
Female	203(46,3)	172(84,7)	23(11,3)	8(3,9)	0.155
Male	235(53,7)	182(77,4)	39(16,6)	14(6)	
Total	438	354(80,8)	62(14,2)	22(5)	
Age					
0-24 month	38	31(81,6)	3(7,9)	4(10,5)	0.241
1-5 year	247	195(78,9)	41(16,6)	11(4,5)	
> 5 year	153	128(83,7)	18(11,8)	7(4,6)	
Season					
Spring	102	90(25,4)	6(9,7)	6(27,2)	0.250
Summer	67	55(15,5)	12(19,4)	0	
Autumn	92	64(18)	21(33,9)	7(31,8)	
Winter	177	145(41)	23(37)	9(41)	
Total	438	354	62	22	

354 of these patients had only rotavirus antigen positivity (80.8%), 62 had only adenovirus antigen positivity (14.2%), and 22 (5%) had both adeno and rotavirus antigen positivity (5%).

74 (16.9%) of the patients were hospitalized and hospitalization period was 3.2±1.67 days. 5 of those with positive adenovirus antigen (8.1%), 6 of those with adeno and rotavirus antigen positivity (27.3%), and 63 of those with positive rota antigen (17.8%) were hospitalized. The average duration of hospitalization was 3.22±1.65 days for patients with positive rotavirus antigen, 3.83±2.14 days for patients with rota and adenovirus positivity, and 2.2±1.1 days for patients with positive adenovirus antigen. There was no significant difference between the groups in terms of length of stay and positivity for rota and / or adeno virus (p = 0.250) (Table 2).

Table 2: Distribution of rota and / or adeno virus antigen positivity in hospitalized patients

Inpatient	Number of cases	Rotavirus	Adenovirus	Rota and adenovirus	p
Number of patients	74(16,9)	63(17,8)	5(8,1)	6(27,3)	0,070
Hospitalization period (day)	3,2±1,67	3,22±1,65	2,2±1.1	3,83±2,14	0,250

When CBC parameters of discharged and inpatient patients were examined, a statistically significant difference was found between neutrophil, lymphocyte and NLR values (p <0.01). There was also a statistically significant difference between CRP and platelet results (p <0.005) (Table 3).

Table 3: Distribution of laboratory parameters in patients hospitalized and discharged

	Discharged from hospital (median/IQR)	Hospitalization (median/IQR)	P
WBC (10 ⁶ /mL)	9,8(3,8/39,9)	9,8(4,1/26,5)	0,587
RBC (10 ⁶ /mL)	4,6(2,2/13)	4,6(3,4/5,80)	0,187
HGM (g/dl)	12(3,8/39,5)	11,7(9,0/15,9)	0,099
HCT (%)	36,8(11/335)	36(29/46,5)	0,264
MCV (fl)	81(34/186)	80(61/108)	0,520
PLT (10 ³ /mL)	312(73/772)	351(140/770)	0,028
NEU (%)	61(9,4/449)	46(7,2/90)	<0,001
LYM (%)	25(2,9/75,5)	34,5(3,8/78,9)	<0,001
NEU	5,6(0,1/32)	4,5(0,6/17)	0,021
LYM	2,3(0,2/12,4)	3,1(0,6/9,4)	<0,001
CRP (mg/dL)	2,9(0,1/134)	1,7(0,1/298)	0,034
NLR	2,36(0,1/38)	1,38(0,1/21,7)	<0,001

NLR : Neutrophil / lymphocyte ratio
iQR: InterQuartile Range

When considered the variability between NLR and groups, NLR of patients with positive rotavirus antigen (n = 227) was 4.9±5.3, NLR of patients with positive rota and adenovirus antigen (n = 9) was 0.75±0.96 and NLR of patients with positive adenovirus antigen (n = 29) was 2.29±2.05 (Figure 2).

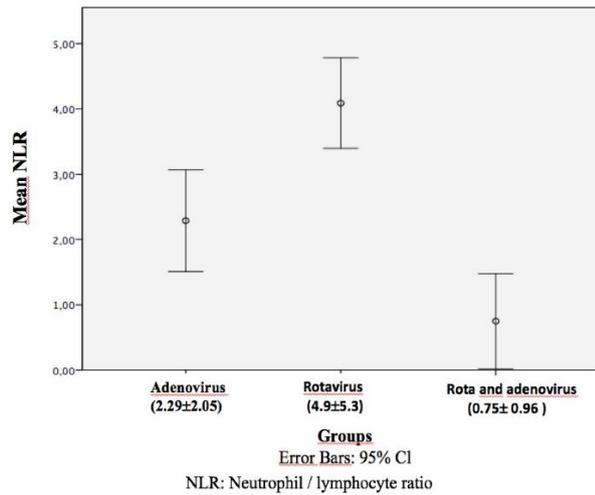


Figure 2: Graph of distribution between NLO and adeno and/or rotavirus antigen positivity

There was a statistically significant difference between the groups in terms of hospitalization of patients with NLR ($p < 0.001$) (Table 4). NLR of inpatients was 2.60 ± 3.73 and NLR of outpatients was 4.23 ± 5.37

Table 4: Distribution of NLR in hospitalized patients with rota and / or adeno virus antigen in stool

NLR	n	mean±SD	Median (Min-Max)	p
Rotavirus(+)	227	4,09±5,3	2.20(0.5-38)	
Rota and adenovirus(+)	9	0,75±0,96	0.46(0.09-2.44)	<0.001
Adenovirus (+)	29	2,29±2,05	1.73(0.37-8.33)	

NLR: Neutrophil / lymphocyte ratio
SD: standard deviation

In terms of NLR and hospitalization of patients, there was no statistically significant difference (0.070) in 5/62 (8.2%) of those with positive adenovirus antigen, 63/354 (17.8%) of those with positive rotavirus antigen, 6/22 (27%) of those with positive rota and adenovirus antigen (0.070).

However, when the groups were compared among themselves, there was only a statistically significant difference between the adeno and rotavirus antigen positive group and the adenovirus antigen positive group (0.023). There was no statistically significant difference between rota and adenovirus antigen positive group and rotavirus group (0.266). In addition, No statistically significant difference was found between the adenovirus and rotavirus groups (0.056). (Table 5)

Table 5: Distribution of NLR between groups in inpatients

NLR	Rotavirus	adenovirus	Rota and adenovirus	P
	Negative	Pozitive	Pozitive	0,023
inpatient	Pozitive	Negative	Pozitive	0,266
	Pozitive	Pozitive	Negative	0,056

NLR: Neutrophil / lymphocyte ratio

DISCUSSION

Our study was carried out in the emergency department of a third level academic education and research hospital, where approximately 400,000 adult and pediatric patients are admitted annually. Every year, approximately 9000 children admitted to our emergency department with gastroenteritis complaints are asked for rotavirus and adenovirus examinations in stool. During our study, rota and / or adenovirus antigen positivity was detected in 4.48% of these patients. Our study included 438 patients with acute gastroenteritis who had a positive rota and / or adenovirus antigen in stool between 01.01.2018 and 01.31.2019. Out of 438 patients 203 (46.3%) were female and 235 (53.7%) were male. The average age was 4.03 ± 3.65 .

In various studies conducted in our country, it has been reported that there is no gender difference in the frequency of viral gastroenteritis (11). In our study, no statistically significant difference was found in both genders in terms of antigen positivity in accordance with other studies.

74 (16.9%) of the patients were hospitalized and hospitalization period was 3.2 ± 1.67 days. However, clear information about the duration of hospitalization of patients with rota and adenovirus antigen positivity was not available in the literature so our study can be significant in terms of providing information about the issue. Although the factors affecting the duration of hospitalization in pediatric gastroenteritis vary considerably, the decision of the clinician is of greater importance.

In our study, rotavirus antigen positivity was found in 354 patients (%80.8), adenovirus antigen positivity in 62 (14.2%) and both adenovirus and rotavirus antigen positivity in 22 (5%) patients (Figure 3).

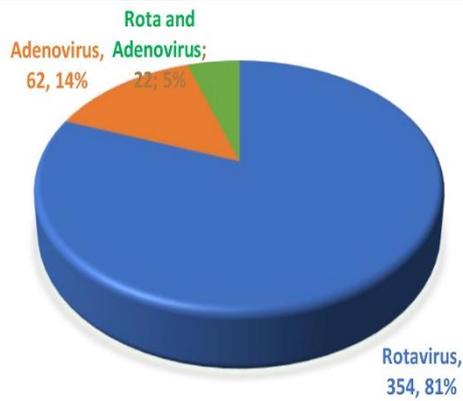


Figure 3: Distribution graphic of patients with rotavirus and/or adenovirus antigen positivity in stool

In studies conducted in different countries, it has been reported that rotavirus is a factor in 10% to 70% of viral gastroenteritis cases (12). Adenovirus is also responsible for 2% to 20% of viral gastroenteritis cases (13). Enteric adenoviruses are in second place after rotaviruses as the cause of acute and prolonged diarrhea in children. In a study conducted by Cruz JR et al. adenovirus cases were detected three times higher than rotavirus. However, this was ascribed to the climate of Guatemala, where the study was conducted (14). In studies conducted in our country, the frequency of rotavirus infection has been reported to be between 20-53% (15). In our study, in accordance with other studies performed in our country, rotavirus antigen positivity was more common in stool, while the incidence was higher. We think this is due to the geographical and economic reasons of our region. We think this is due to the geographical and economic conditions of the region. In our study, the number of patients with adenovirus antigen positivity was found to be similar compared to results of the studies conducted in other countries.

Several factors coexist in gastroenteritis and virus-virus association is found most frequently (14). Some studies reported that the coexistence of rotavirus and adenovirus antigen was between 0.4% and 7.2% (16). In our study, the rates of rotavirus and adenovirus antigen coexistence were similar to other studies.

Rotavirus causes two million children to be hospitalized annually in children under the age of five (17). Especially as a result of vomiting, dehydration and metabolic acidosis developing in this age group, two million hospitalization and 800

thousand deaths are reported every year in the world (18).

In our study, 5 (8.1%) of those with positive adenovirus antigen, 6 (27.3%) of those with adeno and rotavirus antigen positivity and 63 (17.8%) of those with positive rotavirus antigen were treated as inpatients. There was no statistically significant difference between these three groups ($p = 0.070$).

In a study conducted in 63 countries by Parashar et al. 33-49% of children with diarrhea were reported to be admitted to hospital due to rotavirus (19). Jaha et al. demonstrated that 34.4% of children treated for diarrhea were diagnosed with rotavirus. It was also reported by Nitsch-Osuch et al. that 24% of the patients hospitalized were the diagnosed with rotavirus enteritis (20, 21). In a study conducted in Europe and involving many countries, rotavirus antigen positivity in children with diarrhea was reported to be 27-52% (22). The low rate in our study suggests that it is due to the regional and socioeconomic conditions in our country. Adenovirus-induced diarrhea rates are less frequent and have been reported to be 4.8-20% (23). The frequency of enteric adenovirus in inpatients was compatible with the literature.

Regarding hospitalization times, the average value was 3.22 ± 1.65 days for patients with rotavirus antigen positive, for patients with rota and adenovirus positivity 3.83 ± 2.14 , and for patients with adenovirus antigen positive 2.2 ± 1.1 . There was no significant difference between the groups in terms of length of stay and rota and / or adenovirus positivity ($p = 0.250$). Similar to our study, the duration of hospitalization due to rotavirus was found to be 3.2 days on average in a study conducted in Mexico (24).

NLR has been found to be significant in the prognostic follow-up of diseases such as acute coronary syndrome, ulcerative colitis, diabetes, obstructive sleep apnea, and diseases, including Sjogren's syndrome and systemic lupus erythematosus, where inflammatory activity is predominant. (28-33).

Considering the variability between NLR and groups, patients with positive rotavirus antigen in the stool ($n = 227$) were calculated as 4.09 ± 5.3 , patients

with a positive rota and adenovirus antigen (n = 9) were 0.75 ± 0.96 and patients with positive adenovirus antigen (n = 29) were 2.29 ± 2.05 . There was a statistically significant difference between the groups in terms of NLR ($P < 0.001$) (Figure 1). There was also a statistically significant difference between the groups in terms of NLR and whether the patients can be hospitalized (2.59 ± 3.72 and 4.22 ± 5.36 , respectively) ($p < 0.001$).

There was no significant difference between the three groups (adenovirus group 5/62 (8.2%), rotavirus group 63/354 (17.8%), rota and adenovirus group 6/22 (27.3%)) in terms of NLR and hospitalization of patients (0.070). However, when groups were compared, a statistically significant difference was found between adeno and rotavirus and those with positive adenovirus antigen (0.023). There was no statistically significant difference between the rota and those with positive rota and adenovirus (0.266). No statistically significant difference was also found between adeno and those with rotavirus antigen positive (0.056).

Increased NLR is associated with the severity of inflammation and poor prognosis in the literature. However, the results in our study are contradictory with the literature in terms of hospitalization. The reason for this may be lower number of sample. Factors determining the necessity of hospitalization of viral gastroenteritis should also be considered. The main indicator of the need for hospitalization in viral gastroenteritis is the severity of symptoms, and the severity of inflammation does not always correlate with the severity of symptoms. However, in order to make more accurate explanations on this issue, standardized studies with higher patient numbers are needed.

We could not determine the objective findings of the admission criteria since our study is a retrospective study and the decision to hospitalization is made by different physicians. This situation may also have depended on the subjective approaches of physicians and affected our results.

Conclusion

Nowadays, the importance of laboratory tests is increasing in the diagnosis, follow-up, determination of prognosis and selection of medical treatments to be applied. One of these lab tests is NLR, which has

grown in popularity recently. NLR has been used as an indicator of inflammation in most diseases. Our study can be significant from this aspect. Due to its low cost, easy applicability and high sensitivity, NLR may be a method that can be taken into consideration in terms of service hospitalization in children with diarrhea who has a positive rota and / or adenovirus antigen positivity in stool. It should be regarded that the main provision of the need for hospitalization in viral gastroenteritis is the severity of the patients' symptoms rather than the severity of inflammation. Further studies are needed to be carried out on this subject.

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