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# Analysis of Hemogram and C-Reactive Protein in Viral Gastroenteritis: Insights into Inflammatory Response

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**Abstract: Background**: Acute viral gastroenteritis remains a leading cause of health care cost globally, prompting the need for basic diagnostic strategies. Objectives: This study aims to assess the impact of viral gastroenteritis on hemogram and C-reactive protein. **Methods**: By conducting a retrospective study, three groups of children diagnosed with gastroenteritis (rotavirus positive, adenovirus positive and rota/adenovirus negative group) were compared in terms of hemogram parameters and C- reactive protein. **Results**: Among 756 children with gastroenteritis, 7.9% of patients were rotavirus positive and 6.5% of them were adenovirus positive. Our findings disclosed a statistically significant association between low lymphocyte (2.2 ± 1.45) and MPV value (7.38 ± 0.4 fL) with rotavirus gastroenteritis. Also, the analysis revealed a high neutrophil/lymphocyte ratio (2.8± 2.1) in rotavirus group. However, our study did not reveal any prominent laboratory marker that serves as a distinctive feature of adenovirus unlike rotavirus. **Conclusions**: In conclusion our research highlights the potential of decreased mean platelet volume and lymphopenia as diagnostic markers for rotavirus gastroenteritis.

**Keywords:** rotavirus; adenovirus; children; gastroenteritis; mean platelet volume; neutrophil/lymphocyte value

## 1. Introduction

Acute gastroenteritis (AG) is a prevalent infection that significantly impacts the health and well-being of children globally. It's a common cause of morbidity and can lead to dehydration, hospitalization and even death, especially in developing countries [1]. AG in childhood is primarily caused by bacterial, viral and parasitic infections. Over the past few years, as hygiene conditions and sanitation have improved, bacterial causes of AG have decreased, whereas viral causes have shown an increase. Rotavirus, adenovirus, astrovirus and norovirus are the most common viral causes in childhood gastroenteritis. Contaminated food and water, poor hygiene practices and close contact with infected individuals are common modes of transmission. [2-4]. The hallmark symptoms of AG include vomiting, diarrhea, abdominal pain and fever. In fact, it's hard to distinguish viral causes from other reasons. Several laboratory methods can be used as diagnostic tools such as culture, molecular or serological techniques [4]. Despite these different laboratory methods, diagnosis can be challenging in resource limited places, particularly far from city centers. Consequently, basic methods like hemogram or acute phase reactants would help the clinician. Acute phase reactants are proteins that the liver produces in response to inflammation, trauma or tissue injury and can be classified into positive and negative acute phase reactants [5]. Positive acute phase reactants such as C-reactive protein (CRP) or fibrinogen increase in concentration during inflammatory situations. Opposite to this, negative markers, including albumin or transferrin decrease in concentration [6]. Elevated CRP levels suggest an ongoing inflammation and widely used for diagnosis and monitoring response to treatment. AG triggers a robust immune response in the

body, leading to the production of markers like CRP. In the diagnosis of gastroenteritis, hemogram and CRP evaluation may be useful in determining the causative agent and can help the clinician to avoid unnecessary antibiotic use. The objective of this study is to assess hemogram parameters and C- reactive protein values in acute viral gastroenteritis in childhood.

## 2. Materials and Methods:

The study was conducted in Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital between 2013-2016. After obtaining the necessary approval from the ethics committee (date:15.09.2017 no:132) children who presented to our hospital's emergency department with a diagnosis of AG were assessed. Patients aged 1 month to 18 years with diarrhea (loose or watery stools more than 3 times in a day) lasting less than 2 weeks, and who had undergone rotavirus and adenovirus antigen tests, hemogram, CRP evaluations completely were included. Patients who have bacterial growth in stool culture and patients with underlying chronical diseases or coinfections were not included. Also, children who have both adenovirus and rotavirus antigens positive in stool were excluded. The adenovirus and rotavirus antigen tests in stool samples were examined using the immunochromatographic method. After incorporating all children with AG, those with positive stool culture results were excluded. The remaining patients were categorized into three groups; Adenovirus positive (AP), Rotavirus positive (RP), Adenovirus-rotavirus negative (ARN). These groups were compared in terms of demographic values, hemogram parameters and C- reactive protein. Data were analyzed, tabulated, and subjected to using the Statistical Package for Social Sciences (SPSS, version 26). The continuous data were displayed as mean ± SD. At the same time, categorical data were illustrated as numbers and percentages. The Kolmogorov-Smirnov test of normality was utilized to test the normality hypothesis. A p-value of $< 0.05$ was considered statistically significant.

## 3. Results

Seven hundred sixty-five children were admitted to emergency service with AG during the three-year study period. Children who had a chronic illness, trauma, other inflammatory situations or regular medication usage were excluded. Also patients who diagnosed with bacterial or parasitic AG were not included. Sixty-one (7.9%) of them were diagnosed with rotavirus while 50 (6.5%) children had a positive stool antigen test for adenovirus. A total of 112 children was negative for adenovirus and rotavirus. Female, male ratio was 1,02. The median age was $3 \pm 0.9$ years. Most of the children was aged under 2 years (40.6%) and 61.5% of patients was under 3 years. The median duration of hospital stay was 3,5±1,2 days. Comparison between 3 groups (AP, RP and ARN) are summarized in Table 1. Our findings demonstrate no significant difference between 3 groups in terms of age, gender or clinical features such as fever or abdominal pain rates. Regarding laboratory results, a few remarkable aspects were present. Mean MPV value was $7.38 \pm 0.4$ fL in rotavirus group while $7.91 \pm 0.75$ in adeno positive group and $8.1 \pm 0.8$ RAN group. In addition, mean lymphocyte value in rotavirus positive group was $2.190 \pm 1.740$ which is statistically significantly lower than adenovirus group and RAN group. (P < 0,05) When neutrophil/lymphocyte ratio (NLR) was compared between 3 groups, rotavirus group has a higher value (P < 0,05)

**Table 1. Comparative Assessment of Demographic and Laboratory Features within Groups.**

|  | Rotavirus positive | Adenovirus positive | Rota/adeno negative | *p* |
|---|---|---|---|---|
| Age (months) | 32.6 ± 30.7 | 38.64 ± 36.7 | 35.53 ± 30.6 | 0,25 |
| Female/male | 1.1 | 0.9 | 1.03 | 0,17 |
| Vomiting rate | 91.2% | 89.8% | 88% | 0,64 |
| Fever rate | 29.5% | 30.7% | 28% | 0,32 |
| Abdominal pain rate | 32.7% | 34% | 31.4% | 0,571 |

| | | | |
|---|---|---|---|
| C-reactiveprotein (mg/dl) | 1.1±1.25 | 0.91±1.46 | 1.004 ± 1.61 | 0,81 |
| Hemoglobin (g/dl) | 11.2 ±1.4 | 11.53±1.32 | 11.4 ±0.95 | 0,587 |
| White blood cell | 11.3±5.04 | 10.32±4.04 | 9.7±4.6 | 0,75 |
| Neutrophil(10⁹/l) | 5.4±2.78 | 4.9±3.05 | 5.1±2.86 | 0,32 |
| Lymphocyte(10⁹/l) | 2.2±1.45 | 2.9±1.65 | 3.2±1.89 | P < 0,05 |
| Platelet count(10⁹/l) | 301.754±65.213 | 298.546±72.333 | 327.530± 62.435 | 0,38 |
| Neutrophil/Lymphocyte | 2.8±2.1 | 2.4±1.9 | 2.0±1.75 | P < 0,05 |
| Mean cell volume (fL) | 75.48± 5.13 | 76.17±6.34 | 74.1±7.7 | 0,51 |
| Mean platelet vol (fL) | 7.38±0.09 | 7.91±0.75 | 8.1±0.8 | P < 0,05 |

(mg/dl: milligram/deciliter, g/dl: gram/deciliter, fL: femtoliter).

## 4. Discussion

Acute viral gastroenteritis still remains significant morbidity, health care cost and mortality in especially in developing countries with limited access to clean water and healthcare facilities. Especially rotavirus is a highly contagious, vaccine-preventable virus that affects infants and young children and a leading cause of severe diarrhea and dehydration worldwide [7]. In some regions where rotavirus vaccination is a part of national immunization program, a decline in rotavirus incidence has been reported [8]. However, it's worth noting that rotavirus remains the predominant cause of AG in Turkey [9]. Likewise, rotavirus (7.9%) is more common than adenovirus (6.5%) in our study. Unfortunately, due to limited resources, we couldn't investigate other common viruses such as norovirus. In the present study, the 3rd group (Adeno and rotavirus negative) probably consists of viruses we couldn't identify, such as norovirus and astrovirus. While methods such as real time PCR and antigen detection can facilitate swift diagnosis of viral AG, it may not be feasible for every center to have access to these methods. In regions with limited access to detailed laboratory examination, complete blood count and acute phase reactants can provide clinicians with valuable diagnostic clues about rotavirus or adenovirus gastroenteritis. Subsequently, studies investigating laboratory markers in acute gastroenteritis focus on hemogram parameters such as mean platelet volume because of its simplicity and low price [10].   MPV refers to the average size of platelets in blood and is an important indicator of platelet activity and function. MPV value seems to be influenced by many factors like connective tissue diseases, smoking, cerebrovascular diseases or inflammation [11]. Yet, there is a paucity of literature about infection-MPV relationship. Mete et al and Zhang et al found a correlation between decreased MPV and rotavirus gastroenteritis in their studies, similar to us [12,13]. In another study, low MPV level was found to be correlated with *Entamoeba histolytica* gastroenteritis [14]. However, there are some reports on MPV-infection relationship that have yielded disparate results. Such as MPV was found increased in urinary tract infection and hepatitis B [15,16]. These discrepancies among MPV value may be associated with the inflammation degree. The alteration in MPV value is thought to be a result of the thrombopoiesis process. In cases of mild inflammation, it's suggested that MPV increases due to the larger size of newly produced platelets, while in high grade inflammation, MPV is claimed to decrease due to platelet consumption [11]. If we consider adenovirus positive group in our research, we should point out that no statistically significant data was found. Adenovirus, is a type of DNA virus capable of causing various diseases, including respiratory tract infections, conjunctivitis and gastroenteritis following rotavirus. Nascimento et al reported that, adenovirus is most common statistically significant between 6- 24 month in childhood (8). In our research, although adenovirus is most commonly seen between 0-6 months of age, no statistically significant difference was found comparing other age groups. Additionally, our study did not reveal any prominent laboratory marker that serves as a distinctive feature of adenovirus unlike rotavirus. In fact, there was a little knowledge about MPV-adenovirus relationship or hematological parameters in adenovirus AG in

literature. Lymphopenia and viral infections often have a close association, cause some viruses can damage lymphocyte production and function. A multitude of investigations have probed the intricate relationship between viruses and lymphocyte count, yielding divergent mechanisms such as cell death, elevated cytokines or inhibition of lymphopoiesis [17]. Our findings demonstrate a significant correlation between rotavirus gastroenteritis and lymphopenia. Zhang et al. found lymphocyte and MPV values decreased in rotavirus gastroenteritis, similar to our data [13]. In an alternate analysis [18] Wang et al stated the lack of information about lymphocyte regulation in rotavirus gastroenteritis and reported B-cell activation and altered T-lymphocyte function in this group. Hence, further investigations about lymphocyte subtypes in rotavirus infection is warranted to elucidate the short- and long-term effects of rotavirus in immune system. Neutrophil/lymphocyte ratio stands as a simple and cost-effective marker that reflects the severity of immune-inflammatory reaction. High NLR value (2.8±2.1) is remarkable in rotavirus positive group in our research. It has been stated the NLR is around 2-3 in low grade inflammation whereas it's above 3 in higher grade of inflammation (19). Çelik et al. reported a higher NLR in rotavirus gastroenteritis rather than adenovirus similar to us (20). Meanwhile, relative to our results in this study a greater mean NLR value was present (4.09±5,3) in Çelik's study. These variations might be associated with the diverse spectrum of gastroenteritis severity. While our study provides some valuable insights, it's important to acknowledge limitations such as retrospective nature and absence of a healthy control group. Also, APN group was a heterogenic group which is probably consisted of other viruses such as norovirus, astrovirus. Sadly, we couldn't investigate these viruses. Previous studies have provided valuable insights into, yet certain gaps persist in our knowledge. In our study, MPV value was found significantly low in cases of rotavirus gastroenteritis. This may help us to diagnosis of rotavirus. Rapid and accurate identification of rotavirus not only guides appropriate management but also plays a pivotal role in preventing the spread of the virus in community. For future studies, findings from different markers in blood or stool and serial MPV measurements would contribute to a better understanding of viral gastroenteritis.

## References

1. Troeger C, Blacker B, Khalil IA, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study. *Lancet Infect Dis*, 2018;18(11):1211-28.
2. Elliott EJ. Acute gastroenteritis in children. *BMJ*, 2007 Jan 6;334(7583):35-40**.**
3. Lian Y, Wu S, Luo L, et al, Epidemiology of Norovirus Outbreaks Reported to the Public Health Emergency Event Surveillance System, China, 2014‒2017. *Viruses*. 2019 Apr 11;11(4):342.
4. Ramani S, Kang G. Viruses causing childhood diarrhoea in the developing world. *Curr Opin Infect Dis* .2009; 22: 477-482.
5. Khalil RH, Al-Humadi N. Types of acute phase reactants and their importance in vaccination. *Biomed Rep*. 2020 Apr;12(4):143-152.
6. Kushner I. The phenomenon of the acute phase response. *Ann N Y Acad Sci*,1982;389:39-48.

7.   Caddy S, Papa G, Borodavka A, Desselberger U. Rotavirus research: 2014-2020. *Virus Res*. 2021 Oct 15;304:198499.

8.   do Nascimento LG, Fialho AM, de Andrade JDSR, de Assis RMS, Fumian TM. Human enteric adenovirus F40/41 as a major cause of acute gastroenteritis in children in Brazil, 2018 to 2020. *Sci Rep*. 2022 Jul 2;12(1):11220.

9.   Ozsari T, Bora G, Kaya B, Yakut K. The Prevalence of Rotavirus and Adenovirus in the Childhood Gastroenteritis. Jundishapur *J Microbiol*. 2016 Apr 27;9(6):e34867.

10.  Tanju C, Ekrem G, Berksoy, Emel A, Nur A. Mean platelet volume as a negative marker of inflammation in children with rotavirus gastroenteritis. *Iran J Pediatr*. 2014 Oct;24(5):617-22. Epub 2014 Oct 28.

11.  Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? *Curr Pharm Des*. 2011;17(1):47-58.

12.  Mete E, Akelma AZ, Cizmeci MN, Bozkaya D, Kanburoglu MK. Decreased mean platelet volume in children with acute rotavirus gastroenteritis. *Platelets*. 2014;25(1):51-4.

13.  Zhang C, Li G, Zhang H, Zhang H, Fei Y. Decreased lymphocyte to monocyte ratio and increased neutrophil to lymphocyte ratio observed in rotavirus-positive acute gastroenteritis in children: a retrospective study. *Ann Clin Lab Sci*. 2020; 50(4), 450-456.

14.  Matowicka-Karna J, Panasiuk A. Does anti-parasitic treatment normalize platelets morphology in patients infested with Entamoeba histolytica? *Rocz Akad Med Bialymst*. 1996;41(2):258-67.

15.  Lee IR, Shin JI, Park SJ, Oh JY, Kim JH. Mean platelet volume in young children with urinary tract infection. *Sci Rep*. 2015 Dec 15;5:18072.

16.  Hu Y, Lou Y, Chen Y, Mao W. Evaluation of mean platelet volume in patients with hepatitis B virus infection. *Int J Clin Exp Med*. 2014 Nov 15;7(11):4207-13.

17.  Guo Z, Zhang Z, Prajapati M, Li Y. Lymphopenia Caused by Virus Infections and the Mechanisms Beyond. *Viruses*. 2021; 13(9):1876.

18.  Wang Y, Dennehy PH, Keyserling HL et al. Rotavirus infection alters peripheral T-cell homeostasis in children with acute diarrhea. *J Virol*. 2007 Apr;81(8):3904-12.

19.  Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. *Bratisl Lek Listy*. 2021;122(7):474-488.

20.  Çelik E, Halhalli HC, Şancı E (2020). The Effectiveness of Neutrophil/Lymphocyte Ratio in Hospitalization of Childhood Viral Gastroenteritis. *Kocaeli Med J*, *9*(3), 111-119.