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The role of the neutrophil/lymphocyte ratio in distinguishing viral, bacterial, and parasitic acute gastroenteritis: A prospective study

Furkan Yilmaz[1]✉, Cemil Kavalci[2]

[1]*Emergency Medicine Department, Ankara Bilkent City Hospital, Ankara, Turkey*

[2]*Emergency Medicine Department, Health Science University, Antalya Training and Research Hospital, Antalya, Turkey*

ABSTRACT

Objective: To investigate the diagnostic value of the neutrophil/lymphocyte ratio, which has not been studied sufficiently to determine the cause of acute gastroenteritis worldwide.

Methods: The prospective, observational study included patients diagnosed with acute gastroenteritis who were treated at Dışkapı Yıldırım Beyazıt Application and Research Center, Emergency Medicine Clinic between 1 September 2020 and 31 May 2021. Demographic characteristics, as well as neutrophil count, lymphocyte count, white blood cell count, and the neutrophil-to-lymphocyte ratio, were compared across the viral, bacterial, and parasitic acute gastroenteritis groups.

Results: A total of 168 acute gastroenteritis patients, 31 of whom had parasitic, 39 bacterial and 98 viral etiologies, were included in this study. Neutrophil/lymphocyte ratio was 2.73 (4.03) in the viral acute gastroenteritis group, 4.58 (8.61) in the bacterial acute gastroenteritis group, and 4.52 (5.49) in the parasite acute gastroenteritis group. A statistically significant difference was found among the groups regarding neutrophil/lymphocyte ratio (P=0.022). However, *post-hoc* analysis revealed no statistically significant differences in the neutrophil-to-lymphocyte ratio among the groups (P>0.05).

Conclusions: Neutrophil/lymphocyte ratio alone cannot distinguish etiological causes in patients admitted to the Emergency Medicine Clinic diagnosed with acute gastroenteritis.

KEYWORDS: Acute gastroenteritis; Neutrophil/lymphocyte ratio; Infectious disease

1. Introduction

As a result of inflammation of the stomach, small intestine, and large intestine, the clinical condition manifested by the combination of abdominal pain, nausea, vomiting, cramps, and diarrhea is gastroenteritis. If it lasts less than 14 days, it is called acute gastroenteritis (AGE)[1]. Diarrhea is the second most common cause of death in low-income countries, accounting for 10% of deaths worldwide[2]. 50%-70% of the infectious causes of AGE are viral, 15-20% bacterial and 10-15% parasitic. In addition, drugs such as antibiotics, nonsteroidal anti-inflammatory drugs, antacids, chemotherapeutics, poisonous mushrooms, organophosphates, and foods containing arsenic can also cause AGE[1].

Summary

Question: What is the role of the neutrophil/lymphocyte ratio in determining etiology in patients diagnosed with acute gastroenteritis?

Findings: This study investigated the adequacy of the neutrophil/lymphocyte ratio in hemogram tests without the need for stool examination in cases of acute gastroenteritis, which causes high morbidity and mortality worldwide.

Meaning: The neutrophil/lymphocyte ratio alone is not sufficient, and the direct examination technique in stool is indispensable and still maintains its importance today.

✉To whom correspondence may be addressed. E-mail: autfyilmaz@gmail.com

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Rotavirus and norovirus are the leading viral causes[3]. Transmission occurs quickly *via* the fecal-oral route and shared items[4]. Viral gastroenteritis diagnosis, virus analysis in stool, electron microscopy, various molecular methods, ELISA and other immunological tests are used[5]. Treatment of viral gastroenteritis is mainly based on fluid and electrolyte replacement[3].

Shiga toxin-producing *Escherichia coli*, non-type *Salmonella*, *Campylobacter* and *Shigella* are the four most commonly reported bacterial enteropathogens in the United States. These factors lead to an estimated annual cost of $7 billion[6]. Bacteria cause gastroenteritis through three basic mechanisms: Vomiting and abdominal cramps may occur several hours after ingesting the preformed toxin. Toxin secretion after the relevant microorganism adheres to the intestinal epithelium can cause watery gastroenteritis, resulting in fever without blood or mucus. Dysentery, low volume tenesmus with fever may occur due to invasion of the intestinal mucosa. It contains mucus and pus and may cause abdominal pain in the lower quadrants. Stool microscopy, stool culture, PCR and other molecular methods are preferred in diagnosis[7]. Supportive oral or intravenous rehydration, antibiotic or symptomatic treatment should be considered[8].

The two most common causes of parasitic gastroenteritis are giardia and cryptosporidium. Transmission usually occurs from person to person due to oral ingestion of cysts in contaminated water and food. Nausea, vomiting, abdominal cramps and watery diarrhea may occur. Entamoeba histolytic can cause bloody diarrhea. Stool antigen test, stool culture and endoscopic evaluation are used in diagnosis. Oral and IV rehydration and metronidazole can be used in treatment[9].

Neutrophil lymphocyte ratio (NLR) has been recommended for use in emergency services and some other clinical branches because it has high sensitivity and low specificity and is a simple, fast-responding and easily available stress and inflammation parameter[10]. The fact that NLR is easily accessible and low cost has provided useful guidance to clinics. As a result of the studies, it has been understood that NLR is an easily measurable systemic inflammation parameter. It has started to be used in various clinical conditions including inflammation, tumors and cardiovascular diseases[11]. Many infectious microorganisms provide important information about AGE by calculating the NLR. In addition to clinical evaluations in differentiating AGE cases admitted to emergency departments from other inflammatory diseases, NLR is an essential marker in reaching the diagnosis[12]. In this study, we planned to reveal the diagnostic value of NLR in determining the cause of AGE.

2. Patients and methods

2.1. Study setting

The study was prospectively carried out between 1 September, 2020 and 31 May, 2021 at the Emergency Medicine Clinic of Dışkapı Yıldıeım Beyazıt Health Application and Research Center and the data obtained for the study were analyzed on 8 June, 2021.

2.2. Ethical statement

This study protocol was approved by the Ethics Committee of SBU Dışkapı Yıldırım Beyazıt Health Application and Research Center (SUAM), Ankara, Turkey (Date: 24.08.2020; Approval No: 94/04).

2.3. Inclusion and exclusion criteria

Patients aged 18 years or older diagnosed with AGE voluntarily participated in our study, and they signed an informed consent form. Patients under the age of 18 years, those who had previously used prescription drugs due to AGE diagnosis, those diagnosed with acute abdomen, and those with inflammatory bowel disease, immune deficiency, malnutrition, malabsorption syndrome, and hematological and malignant diseases were excluded from the study.

2.4. Measurements

According to the results of the direct stool examination and stool culture test, viral, bacterial and parasitic agents were identified. Stool samples taken from the patients were evaluated by direct manual examination and stool culture test under the microscope and examined for the presence of erythrocytes, leukocytes, parasites and eggs. Meanwhile, hemogram parameters were examined from the blood sample taken during the first emergency admission of patients presenting with AGE.

The number of patients included in the study was determined using the G power 3.1 package program. The number of patients required to be recruited for a medium effect size, and 80% power was calculated as 168 (α=0.05, β=0.95, effect size=0.3).

2.5. Statistical analysis

The data presented in our study were evaluated statistically using the Statistical Package for Social Sciences (SPSS Inc. Chicago, USA) program. Descriptive data were expressed as the number

(*n*), percentage, mean, standard deviation, and median (IQR). The Kolmogorov-Smirnov test was used to distribute continuous data. When the data were evaluated, it was seen that there was no normal distribution. The *Chi*-square test was used to compare categorical data (age, gender, chronic disease; presence of drug use, stool microscopy). Kruskal-Wallis test was used to compare continuous data white blood cell (WBC), NLR. Mann-Whitney *U* test was used in *post-hoc* evaluation comparing paired groups. A result of $P<0.05$ was accepted as statistically significant.

3. Results

A total of 168 patients diagnosed with AGE were included in our study. In the study, patients were divided into three groups according to the aetiology of AGE. According to the results of stool samples, 98 patients were evaluated in the viral group, 39 patients were in the bacterial group, and 31 patients were in the parasite group (Figure 1).

Of the patients, 71 were female, and 97 were male. Forty-eight patients had a history of chronic disease. Twenty-eight patients diagnosed with hypertension were identified. Forty-three patients had a history of routine drug use. In the stool examination of the patients, it was determined that 51 had a normal appearance, 50 had a watery appearance, and 45 had a liquid appearance. The clinical and demographic findings of the patients are summarised in Table 1. As a result of stool macroscopy examination, a statistically significant difference was detected between the groups ($P=0.000$) (Table 1).

The median NLR value in the viral group was 2.73 (4.03), the median NLR value in the bacterial group was 4.58 (8.61) and the median NLR value in the parasitic group was 4.52 (5.49). In statistical analysis, a significant difference was found in NLR values between groups ($P<0.05$). However, in the *post hoc* analyses we conducted to identify the group that made the difference, we saw that although the median values of the patients in the viral group were lower than those in the other groups, without a significant difference. Hematological parameter values of the patients according to groups are summarised in Table 2.

There was no statistical difference between the groups for the WBC variable ($P=0.207$). There was no statistical difference between the groups regarding the neutrophil variable ($P=0.052$). There was a statistical difference between the groups for the lymphocyte variable ($P=0.043$). A statistical difference was detected between the groups for the NLR variable ($P=0.022$) (Table 2). However, we could not find a statistically significant difference in the pairwise comparisons indicating which group caused the difference.

4. Discussion

As a result of our study, we found a statistically significant difference between the groups in both stool microscopy and lymphocyte and NLR counts. When stool microscopies were examined, it was found that 4 out of 8 cases of bloody diarrhea (50.0%) had bacterial aetiology, and 3 (37.5%) had parasitic aetiology. In the study conducted by La Rocque and colleagues, it was observed that bacterial pathogens caused bloody diarrhea more frequently than other agents[13]. In the study conducted by Graves, it was said that patients presenting to clinical centres with bloody diarrhea should be investigated for the presence of a specific pathogen in acute bacterial gastroenteritis[1]. It was stated in the study by Iturriza *et al*. that viral gastroenteritis is mainly characterized by non-bloody diarrhea[2]. In our research,

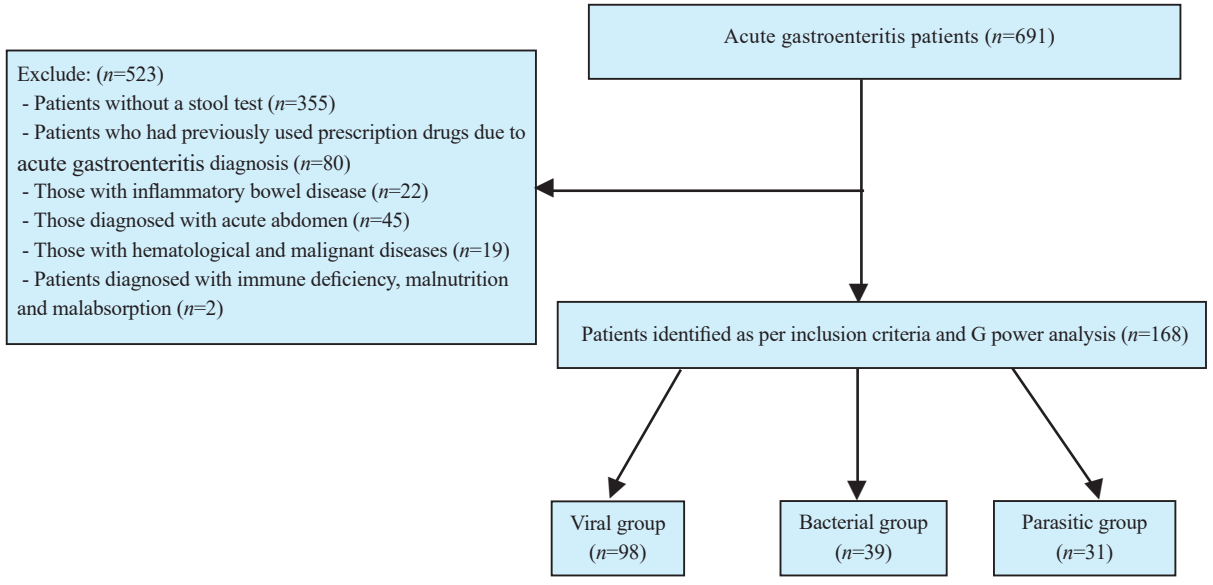

Figure 1. The study flowchart.

Table 1. Patient characteristics.

Variables	Viral etiology (*n*=98)	Bacterial etiology (*n*=39)	Parasitic etiology (*n*=31)	*P*
Age, years, mean±SD	35.9±13.8	46.9±20.4	44.3±19.5	0.147
Sex, *n*, %				
Female	36 (50.7)	19 (26.8)	16 (22.5)	0.223
Male	62 (63.9)	20 (20.6)	15 (15.5)	
Chronic disease, *n*, %				
Yes	23 (47.9)	14 (29.2)	11 (22.9)	0.223
No	75 (62.5)	25 (20.8)	20 (16.7)	
Chronic disease, *n, %*				
Hypertension	10 (35.7)	11 (39.3)	7 (25.0)	0.024
Diabetes mellitus	5 (41.7)	3 (25.0)	4 (33.3)	0.336
Asthma/COPD	3 (37.5)	3 (37.5)	2 (25.0)	0.459
Heart failure	1 (33.3)	1 (33.3)	1 (33.3)	0.661
Coronary artery disease	6 (46.2)	4 (30.8)	3 (23.1)	0.648
Peptic ulcer	7 (50.0)	4 (28.6)	3 (21.4)	0.801
Medicine used, *n*, %				
Yes	23 (53.5)	13 (30.2)	7 (16.3)	0.448
No	75 (60.0)	26 (20.8)	24 (19.2)	
Stool macroscopy, *n*, %				
Normal looking	45 (88.2)	3 (5.9)	3 (5.9)	0.000
Watery looking	34 (68.0)	9 (18.0)	7 (14.0)	
Liquid looking	17 (37.8)	13 (28.9)	15 (33.3)	
Bloody looking	1 (12.5)	4 (50.0)	3 (37.5)	
Mucous looking	1 (7.1)	10 (71.4)	3 (21.4)	

COPD: chronic obstructive pulmonary disease.

bloody diarrhea was less common in viral gastroenteritis cases than bacterial and parasitic gastroenteritis. Bacterial gastroenteritis should be considered more prominently in patients with bloody diarrhea. Our study was found to be compatible with the literature.

When stool microscopy was evaluated, 10 of 14 patients (71.4%) with mucus were found to be of bacterial origin. In the study conducted by Hartmann *et al*., it was stated that stool culture examination is necessary as a standard in cases of blood and mucus in the stool, especially in terms of detecting the agents that cause bacterial gastroenteritis. Bacterial gastroenteritis should be considered primarily in patients presenting with mucus-like defecation complaints. Our research is compatible with the literature[14].

Results of lymphocyte variable: It was calculated as 2 050 (1 463) in the viral group, 1 530 (1 290) in the bacterial group, and 1 890 (1 220) in the parasite group. Our research aimed for the lymphocyte variable to increase significantly in the viral group. It was observed that the results of the lymphocyte variable made a significant difference between the groups (*P*=0.043). In the study by Guo *et al.*, it was stated that most viruses generally cause relative lymphocytosis[15]. Our research is compatible with the literature.

Our study found that NLR values significantly differed statistically between the three groups (*P*=0.022). Still, in our analysis of the group that made the difference, we found that although the NLR rates of the patients in the viral group were low, neither group alone created a statistically significant difference.

In the study conducted by Holub *et al*., the median of NLR calculated in patients diagnosed with bacterial infection was 11.73 (7.73-21.87), and in patients with viral infection, the median was 2.86 (1.95-4.15). In distinguishing bacterial and viral infections, the NLR threshold value was 6.2; sensitivity value was calculated as 91% and specificity value as 96%[16]. Our research is compatible with the literature on this subject. In a study by Zhang *et al*., it was stated that increased NLR value can independently predict endothelial dysfunction in patients with chronic renal failure, peripheral artery occlusive disease, and coronary artery bypass graft[17]. Our study classified 7 of 8 patients (87.5%) with bloody diarrhea in the bacterial and parasitic aetiology groups. Bloody diarrhea, which develops due to the invasion of the relevant pathogen into the intestinal mucosa, is considered an indicator of

Table 2. Hematological values of patients according to groups, median, IQR.

Hematological values	Viral infection	Bacterial infection	Parasitic infection	*H*	*P*
WBC, $10^3/\mu$ L	9 395 (4 413)	9 210 (4 380)	10 110 (5 630)	3.60	0.207
Neutrophil, $10^3/\mu$ L	6 065 (4 360)	7 080 (4 180)	7 010 (6 090)	8.91	0.052
Lymphocyte, $10^3/\mu$ L	2 050 (1 463)	1 530 (1 290)	1 890 (1 220)	11.63	0.043
NLR	2.73 (4.03)	4.58 (8.61)	4.52 (5.49)	14.37	0.022

IQR: interquartile range; WBC: white blood cell; NLR: neutrophil/lymphocyte ratio.

endothelial damage, and our study is compatible with the literature on this subject.

Qu *et al*. reported that Gram-negative bacteria, Gram-positive bacteria, and fungi are effective diagnostic indicators for predicting bloodstream infections[18]. As a result of the evaluation of the use of NLR in some infective diseases such as acute appendicitis; it has been observed that NLR has a superior performance in giving results against WBC and C-reactive Protein. It has also been stated that it provides similar information about infection with some infective parameters such as presepsin and sofa; in fact, NLR is the most practical parameter to calculate among the blood count cell parameters[19]. We believe that by detecting the source of bacterial infection in patients early, progression to sepsis will be prevented, and the benefits to both the patient and the health centres will increase.

In our study, it was found that comparing the NLR values of 3 groups could be influential in determining the cause of AGE; However, in the analysis to determine the group that made the difference, we saw that the NLR values of any group did not make a significant difference on their own. Contradictory results were obtained in our study investigating the role of NLR in determining the aetiology of patients admitted to our Emergency Medicine Clinic with AGE. The fact that NLR has a significant value in the table where only viral, bacterial and parasite groups are evaluated as three groups show that NLR is still insufficient to determine the aetiology in patients diagnosed with AGE, and the direct examination of stool test still has an essential place in diagnosis.

Conflict of interest statement

The authors report no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

Study concept and design: FY and CK; Analysis and interpretation of data: FY, CK; Drafting of the manuscript: FY; Critical revision of the manuscript for important intellectual content: FY, CK; Statistical analysis: CK.

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