İSTANBUL UNIVERSITY PRESS

Çocuk Dergisi - Journal of Child 2023;23(2):113-118
DOI: 10.26650/jchild.2023.1075370

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Children With Rotavirus Positive And Rotavirus Negative Diarrhea

Rotavirüs-Pozitif ve Rotavirüs-Negatif İshali Olan Çocukların Değerlendirilmesi

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Citation/Atıf: Aydın Z, Almis H, Cilasun C, Bucak IH, Turgut M. Evaluation of children with rotavirus-positive and rotavirus -negative diarrhea. Çocuk Dergisi - Journal of Child 2023;23(2):113-118. https://doi.org/10.26650/jchild.2023.1075370

ABSTRACT

Objective: Rotavirus is the most frequent cause of infectious acute gastroenteritis in children and may result in electrolyte imbalance, severe dehydration, hypovolemic shock, and death. Even though improved serological methods for definitive diagnosis exist, these methods may not always be easy to reach. This study aims to evaluate the parameters that help the diagnosis of rotavirus gastroenteritis.

Material and Methods: We retrospectively reviewed 1,539 children aged 1 month to 18 years who had been admitted to our hospital for acute gastroenteritis. Patients were divided into two groups: rotavirus positive and rotavirus negative. There were 745 patients in the RV-positive group and 794 patients in the RV-negative group.

Results: The mean RBC (p=0.005), Hb (p<0.001), Htc (p<0.001), MCV (p<0.001), neutrophil (p=0.001), PLR (p=0.003), NLR (p<0.001), and ELR (p<0.001) levels were significantly lower in the RV-positive group. The mean PLT level (p=0.005) and the mean lymphocyte level (p<0.001) were significantly higher in the RV-positive group.

Conclusion: Several hematological parameters were influenced in rotavirus gastroenteritis. RBC, Hb, Htc, MCV, the mean platelet level, the mean neutrophil level, the mean lymphocyte level, platelet /lymphocyte ratio, neutrophil/lymphocyte ratio, and the eosinophil/lymphocyte ratio could be supportive for rotavirus gastroenteritis.

Keywords: Rotavirus, Gastroenteritis, Child

ÖZ

Amaç: Rotavirüs, çocuklarda en sık görülen ve elektrolit düzensizliği, şiddetli dehidratasyon, hipovolemik şok ve ölümle sonuçlanabilen akut gastroenterit nedenidir. Kesin tanı için geliştirilmiş serolojik yöntemler mevcut olsa da bu yöntemlere ulaşmak her zaman kolay olmayabilir. Bu çalışma rotavirüs tanısına yardımcı olan parametreleri değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Akut gastroenterit nedeniyle hastanemize başvuran 1 ay-18 yaş arası 1539 çocuğu retrospektif olarak inceledik. Hastalar rotavirüs pozitif ve rotavirüs negatif olarak iki gruba ayrıldı. RV-pozitif grupta 745 hasta ve RV-negatif grupta 794 hasta vardı.

Bulgular: Ortalama RBC (p=0,005), Hb (p<0,001), Htc (p<0,001), MCV (p<0,001), nötrofil (p=0,001), platelet lenfosit oranı (p=0,003), nötrofil lenfosit oranı (p<0,001), eozinofil lenfosit oranı (p<0,001) seviyeleri RV-pozitif grupta anlamlı olarak daha düşüktü. Ortalama platelet düzeyi (p=0,005) ve ortalama lenfosit düzeyi (p<0,001) RV-pozitif grupta anlamlı olarak daha yüksekti.

Sonuç: Rotavirüs gastroenteritinde birçok hematolojik parametre etkilenmiştir. RBC, Hb, Htc, MCV, ortalama trombosit düzeyi, ortalama nötrofil düzeyi, ortalama lenfosit düzeyi, trombosit/lenfosit oranı, nötrofil/lenfosit oranı, eozinofil/lenfosit oranı ve rotavirüs gastroenteriti için destekleyici olabilir.

Anahtar Kelimeler: Rotavirüs, Gastroenterit, Çocuk

INTRODUCTION

Acute gastroenteritis (AGE) is the most important public health problem that can cause morbidity and mortality in childhood (1). It can be infectious or non-infectious (2). Viruses are responsible for approximately 70% of infectious AGE in childhood, and rotavirus (RV) is the most frequent cause of infectious acute gastroenteritis in children under five years of age (3). The rotavirus-related global deaths in children aged less than 5 were estimated to have been 527,000 (475,000 – 580,000) in 2004 (4). Rotavirus leads to severe dehydration, and if it is not managed correctly, eventually may result in mortality. Accurate diagnosis remains very important to ensure proper hydration at the right time and to prevent mortality (2). In addition, diagnosis of rotavirus prevents unnecessary antibiotic use, side effects of antibiotics, and unwarranted cost

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Submitted/Başvuru: 18.02.2023 • **Revision Requested/Revizyon Talebi:** 22.03.2023 • **Last Revision Received/Son Revizyon:** 24.04.2023 • **Accepted/Kabul:** 27.04.2023 • **Published Online/Online Yayın:** 16.06.2023

of treatment (5). Rotavirus can be diagnosed by enzyme-linked immunosorbent assay, latex agglutination, radioimmunoassay, counterimmunoelectro-osmophoresis, polyacrylamide gel electrophoresis, and polymerase chain reaction methods or electron microscopy (3). Even though improved serological methods exist for definitive diagnosis, these methods may not always be easy to achieve, especially in underdeveloped areas. It is known that many hematological changes can occur in viral infections, and whole blood count analysis is a simple and easily available test in many areas (6). For this reason, we wanted to determine hematological clues to differentiate rotavirus gastroenteritis from non-rotavirus gastroenteritis.

MATERIALS AND METHODS

We retrospectively reviewed children ages 1 month to 18 years who were admitted to Adiyaman University School of Medicine Education and Research Hospital's pediatric outpatient clinics or hospitalized with acute gastroenteritis between 2012-2016.

The patients with chronic gastroenteritis or any chronic illness or immune deficiency or malnutrition and newborns were excluded from the study. Chronic gastroenteritis was accepted as diarrhea that lasts for more than 4 weeks (7).

The diagnosis of rotavirus antigens was researched using a qualitative immunochromatographic method (RIDA QuickRota-Adeno-Combi R-Biopharm AG, Germany) in stool samples. The sensitivity and specificity of the test had been reported as 97.8% and 94.4%, respectively.

The patients were divided into two groups. The rotavirus-positive group (RV-positive) consisted of 745 patients, and the rotavirus-negative group (RV-negative) consisted of 794 patients. They were also divided into 5 groups according to age: 1-11 months, 12-23 months, 3-5 years, 5-11 years, and ≥12 years.

The demographic data of the patients (age, gender, months, and seasons that patients visited the hospital), and hematological parameters (White Blood Cell (WBC), Platelet (PLT), Hemoglobin (Hb), Hematocrit (Htc), Mean Corpuscular Volume (MCV), Mean Platelet Volume (MPV), Plateletcrit (PCT), Red blood cell count (RBC), Neutrophil count, Lymphocyte count, Eosinophil count, Basophil count, and Neutrophil / Lymphocyte Ratio (NLR), Platelet / Lymphocyte Ratio (PLR), and Eosinophil / Lymphocyte Ratio (ELR)) were recorded for both RV-positive and RV-negative patients, and were compared.

The whole blood count analyses were performed in a Coulter Sysmex XT-2000i analyzer (Roche Diagnostics GmbH, Mannheim, Germany) in the central laboratory of our hospital.

The WBC, PLT, Hb, Htc, MCV, MPV, PCT, and RBC values were obtained from the whole blood count analyses. PLR, NLR, and ELR were calculated by dividing the numerator by the denominator from the whole blood count analysis.

For WBC 3.7-10.1 K / uL, for RBC 4.06-4.69 K / uL, for Hb 12.9-14.2 g / dl, for Htc 37.7-53.7%, for MCV 81-96 fl, for PLT 155-366 K / uL, for PCT 0.10-0.41%, and for MPV 6.9-10.6 fl values were normal. For CRP 0-0, 82 mg/dl values were normal (8).

Statistical analysis

SPSS v.22.0 was used for statistical analysis. Mann-Whitney U and t-tests were used for independent groups. The relationship between variables was examined by Chi-square analysis and Correlation analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off levels of significant hematological parameters in patients with RV gastroenteritis. The correlation analyses between clinical findings and laboratory values were investigated with the Pearson test for parametric data and the Spearman test for nonparametric data. $p< 0.05$ was considered statistically significant.

RESULTS

There were 745 patients in the RV-positive group and 794 patients in the RV-negative group. There were 421 (57%) boys and 324 (43%) girls in the RV-positive group. There were 469 (59%) boys and 325 (41%) girls in the RV-negative group. The mean age was 1.88±1.74 years (median age: 4.2 years) in

Table 1: Patients' Demographic Data

	Rotavirus-positive (n= 745)	Rotavirus-negative (n=794)
Gender (boys/ girls)	324/421	325/469
Age (mean ± SD)	1.88±1.74 years	2.81±3.03 years
Ages between 1-11 months (n %)	235 (31.5 %)	371 (46.7 %)
Ages between 12-23 months (n %)	336 (45.1 %)	151 (19 %)
Ages between 2-5 years (n %)	138 (18.5 %)	132 (16.6 %)
Ages between 6-11 years (n %)	29 (3.9%)	124 (15.6 %)
Ages greater than 12 years (n %)	7 (0.9%)	16 (2 %)

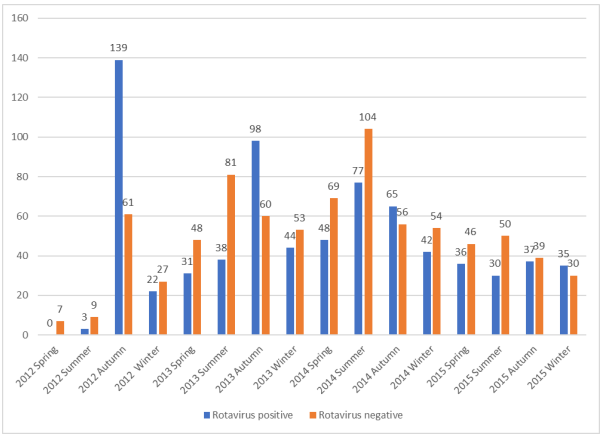

Table 2: Seasonal Distribution of Number of Patients

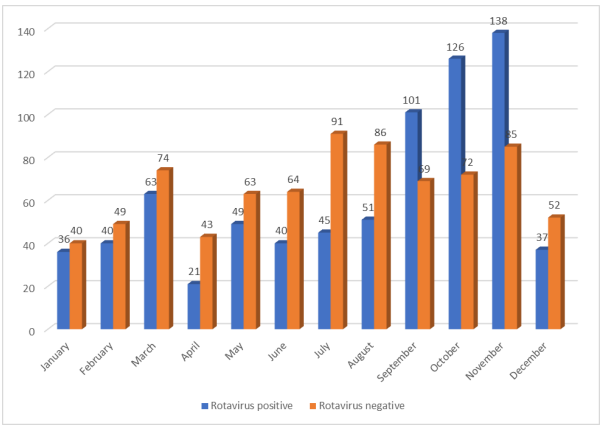

Table 3: Monthly Distribution of Number of Patients

the RV-positive group and 2.81±3.03 years (median age: 5.7 years) in the RV-negative group. No significant difference was found between groups in terms of gender *(p=0.465)* and age *(p=0.062).*

Patients were also divided into 5 groups according to age: 1-11 months, 12-23 months, 3-5 years, 5-11 years, and ≥12 years. Of the patients determined to be RV-positive, 235 (31.5%) were aged 1-11 months, 336 (45.1%) patients were aged 12-23 months, 138 (18.5%) patients were aged 2-5 years, 29 (3.9%) patients were aged 6-11 years, and 7 (0.9%) patients were aged greater than 12 years. Of the patients determined to be RV-negative, 371 (46.7%) patients were aged 1-11 months, 151 (19%) patients were aged 12-23 months, 132 (16.6%) patients were aged 2-5 years, 124 (15.6%) patients were aged 6-11 years, and 16 (2%) patients were aged greater than 12 years. While the greatest number of patients was aged between 12 and 23 months in the RV-positive group, the greatest number of patients was aged between 1 and 11 months in the RV-negative group. Demographic data of the patients are given in **Table 1.**

Three hundred and thirty-nine (45.5%) patients were diagnosed as RV-positive AGE in autumn, 148 (19.9%) in summer, 143 (19.1%) in winter, and 115 (15.5%) in spring. While RV-positive AGE was diagnosed in September, October, and November in particular, RV-negative AGE was diagnosed in July and August in particular. The seasonal distribution of patients is given in **Table 2**, and the monthly distribution of patients is given in **Table 3.**

The mean WBC level was 10.77±4.01 K/uL in the RV-positive group, and 11.05±3.87 K/uL in the RV-negative group. The mean CRP level was 0.79±2.76 mg/dl in the RV-positive group, and 0.98±1.75 mg/dl in the RV- negative group. The mean PCT level was 0.26±0.08% in the RV-positive group, and 0.25±0.08% in the RV-negative group. The mean MPV level was 8.12±1.33 fl in the RV-positive group, and 8.10±1.39 fl in the RV-negative group. White blood cells *(p=0.239),* CRP *(p=0.116),* PCT *(p=0.051),* and MPV *(p=0.864)* were not significantly different between groups.

The mean RBC level was 4.62±0.51 K/uL in the RV-positive group, and 4.68±0.52 K/uL in the RV-negative group. The mean Hb level was 11.68±1.16 g/dl in the RV-positive group, and 12.05±1.34 g/dl in the RV-negative group. The mean Htc level was 34.19±3.53 % in the RV-positive group, and 35.61±3.99% in the RV-negative group. The mean MCV level was 73.94±6.77 fl in the RV-positive group, and 75.23±6.76 fl in the RV-negative group. The mean RBC *(p=0.005),* Hb *(p<0.001),* Htc *(p<0.001),* and MCV *(p<0.001)* levels were significantly lower in the RV-positive group.

The mean PLT level was 346.41±117.48 K/uL in the RV-positive group, and 331.09±111.54 K/uL in the RV-negative group. The mean PLT level was significantly higher in the RV-positive group *(p=0.005).*

The mean monocyte count was 892.19±718.23/ mm^3 in the RV-positive group, and 835.55±695.02/ mm^3 in the RV-negative group. The mean basophil count was 203.87±242.44/ mm^3 in the RV-positive group, and 179.60±209.45/ mm^3 in the RV-negative group. The mean eosinophil count was 133.46±166.81/ mm^3 in the RV-positive group, and 151.49±182.81/ mm^3 in the RV-negative group. The monocyte *(p=0.096),* basophil *(p=0.254),* and eosinophil *(p=0.055)* were not significantly different between groups.

The mean lymphocyte count was 4854.64±2546.84/ mm^3 in the RV-positive group, and 4156.17±2433.37/ mm^3 in the RV-negative group. The mean lymphocyte level was significantly higher in the RV-positive group *(p<0.001).*

The mean neutrophil count was 4887.38±2737.97/ mm^3 in the RV-positive group, and 5526.40±3315.47/ mm^3 in the RV-negative group. The mean NLR level was 1.65±2.04 in the RV-positive group, and 2.12±2.49 in the RV-negative group. The mean PLR level was 0.09±0.07 in the RV-positive group, and 0.11±0.08 in the RV-negative group. The mean ELR level was 0.03±0.06 in the RV-positive group, and 0.04±0.06 in the RV-negative group. The neutrophil *(p=0.001),* NLR *(p<0.001),* PLR *(p=0.003),* and ELR *(p<0.001)* were significantly lower in the RV-positive group. Patients' hematologic parameters are given in **Table 4.**

Table 4: Patients' Hematologic Parameters

Parameter	Rotavirus-positive (n=745)	Rotavirus-negative (n=794)	*P*
Age, years (mean±SD/years)	1.88±1.74	2.81±3.03	*0.062*
Leukocyte (K/uL)	10.75±4.01	11.05±3.87	*0.239*
C-Reactive Protein (mg/dl)	0.79±2.76	0.98±1.75	*0.116*
Red Blood Cell (K/uL)	4.62±0.51	4.68±0.52	***0.005****
Hemoglobin(g/dl)	12.05±1.34	12.05±1.34	***<0.001****
Hematocrit (%)	34.19±3.53	35.61±3.99	***<0.001****
Mean Corpuscular Volume (fl)	73.94±6.77	75.23±6.76	***<0.001****
Platelet (K/uL)	346.41±117.48	331.09±111.54	***0.005****
Plateletcrit (%)	0.26±0.08	0.25±0.08	*0.051*
Mean Platelet Volume (fl)	8.12±1.33	8.10±1.39	*0.864*
Neutrophil (/mm^3)	4887.38±2737.97	5526.40±3315.47	***=0.001****
Lymphocyte (/mm^3)	4854.64±2546.84	4156.17±2433.37	***<0.001****
Monocyte (/mm^3)	892.19±718.23	835.55±695.02	*0.096*
Basophil (/mm^3)	203.87±242.44	179.60±209.45	*0.254*
Eosinophil (/mm^3)	133.46±166.81	151.49±182.81	*0.055*
Neutrophil/Lymphocyte Ratio (NLR)	1.65±2.04	2.12±2.49	***<0.001****
Platelet/ Lymphocyte Ratio (PLR)	0.09±0.07	0.11±0.08	***0.003****
Eosinophil/Lymphocyte Ratio (ELR)	**0.03±0.06**	**0.04±0.06**	***<0.001****

Table 5: Parameters That Defined by ROC Curve Analysis

Parameters	Area under curve	P	Cut off value	Spesifite %	Sensitivite %
Hemoglobin (g/dl)	0.576±0.015	***<0.001****	11.95	54.3	58.2
Hematocrit (%)	0.605±0.014	***<0.001****	35.50	51	64.1
MeanCorpuscular Volume (fl)	0.567±0.015	***<0.001****	75.50	50.8	59.1
Platelet/Lymphocyte Ratio (PLR)	0.563±0.015	***<0.001****	0.084	54.8	56
Neutrophil/Lymphocyte Ratio (NLR)	0.589±0.015	***<0.001****	1.15	55	59.3
Eosinophil/Lymphocyte Ratio (ELR)	0.572±0.015	***<0.001****	0.021	56.3	56.6

Receiver Operating Characteristic (ROC) analysis was performed to determine the optimal cut-off values of Hb, Htc, MCV, PLR, NLR, and ELR values, and their diagnostic efficiency in the presence of rotavirus.

The best cut-off values for the prediction of parameters were 11.95 for Hb, 35.5 for Htc, 75.5 for MCV, 0.84 for PLR, 1.15 for NLR, and 0.021 for ELR. The area under the ROC curve for PLR was 0.563 (95% CI 0.53–0.59). The value of 0.84 had a sensitivity of 56% and a specificity of 54.8%. The area under the ROC curve for NLR was 0.589 (95% CI 0.56–0.61). The value of 1.15 had a sensitivity of 59.3% and a specificity of 55%. The area under the ROC curve for ELR was 0.572 (95% CI 0.54–0.60). The value of 0.021 had a sensitivity of 56.6% and a specificity of 56.3%.

Parameters defined by ROC curve analysis are given in **Table 5.**

DISCUSSION

We retrospectively evaluated 1,539 patients with acute gastroenteritis who had been admitted to Adiyaman University School of Medicine Education and Research Hospital. The male/female ratio in RV-positive patients was 421 (56%) / 324 (44%), and it was observed that there was no difference between the two groups in terms of gender *(p = 0.465).* In addition, the male/female ratio was 1.29 in the RV-positive group. There was no clear explanation for the higher number of male patients in the RV-positive group, and many studies have detected similar differences in terms of gender. The male/female ratio has been reported as 1.63 and 1.97 by Arun et al., and by Fang et al., respectively (9,10).

There was also no difference between the two groups in terms of age ***(****p=0.062).* The mean age of the RV-positive group was 1.88 ± 1.74 years (22.56 ± 20.88 months). The

mean age of children with rotavirus has been reported as 38.74±41.45 months and 15 months by Mete et al. and Dalgic et al., respectively (11,12). In our study, the highest number of rotavirus cases also was observed in children aged 12–23 months. Furthermore, Bozdayi et al. found that 70% of a group of children with rotavirus were under the two of age (13). All these results showed that rotavirus affects children of younger ages who may be easily dehydrated. For this reason, early recognition and appropriate treatment of rotavirus will prevent severe dehydration.

We compared the seasonal variability of RV. Many different national and international results have been reported about the seasonal distribution of rotavirus (14). Sanchez-Fauquier et al. found that rotavirus infection increased during the winter months, especially in January. Tajiri et al. found an increasing rate of rotavirus infection between February and May (15,16). In this study, rotavirus infections were detected mostly in the winter months. This global seasonal variability can be explained by climate changes, countries' levels of development, or the time of vaccination.

There was no difference between the two groups in terms of mean WBC level *(p=0.239)* and mean CRP level *(p=0.116).* Similarly to our study, Green et al. found no difference between rotavirus-positive and rotavirus-negative groups in terms of mean WBC level (17). While the mean CRP level of RV-positive patients was 0.79±2.76 mg/L (normal: 0.1-0.82) in our study, Dalgic et al. reported 18.27±37.43 mg/L (normal <5 mg/L) in their study (12). Higher WBC and CRP values may be found in viral infections. However, very high CRP levels and WBC levels are mostly found in bacterial infections (18). The lack of significant difference in WBC and CRP levels between groups, and the absence of severe elevation of these parameters, suggests that the etiology of the rotavirus-negative group could be the other viruses.

The mean RBC, Hb, Htc, and MCV levels were significantly lower in the RV-positive group *(p<0.001).* Although other causes of anemia were not investigated between the two groups, it might be a rotavirus-induced result. Previous studies have reported that hemoglobin levels may decrease by 1 g/dl or 0.6 g/dl during mild viral infections (19,20). In addition, the mean PLT levels were significantly higher in the rotavirus-positive group *(p=0.005)***.** The reason for high PLT levels in viral infections may be related to many cytokines, such as IL1-IL6, IL8, and GM-CSF (21). On the other hand, the lower Hb levels that exist in the rotavirus-positive group could have played a role in higher PLT levels.

In our study, the mean neutrophil count levels were significantly lower in the RV-positive group *(p=0.001)***,** and the mean lymphocyte count levels were significantly higher in the RV-positive group *(p=0.001)***.** Following this, the mean NLR levels and the mean ELR levels were significantly lower in the RV-positive group *(p=0.001, p<0.001)***.** These results were compatible with each other and can explain the reactive lymphocytosis in viral infections.

CONCLUSION

Several hematological parameters were influenced in rotavirus gastroenteritis. RBC, Hb, Htc, MCV, the mean platelet level, the mean neutrophil level, the mean lymphocyte level, platelet/lymphocyte ratio, neutrophil/lymphocyte ratio, and the eosinophil/lymphocyte ratio could be supportive for rotavirus gastroenteritis.

Ethics approval: The study protocol was approved by the Local Ethical Committee (Protocol Number: 2015/ 09-2) and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Ethics Committee Approval: The study protocol was approved by the Local Ethical Committee (Protocol Number: 2015/ 09-2) and was performed in accordance with the Declaration of Helsinki.

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- Z.A., H.A., M.T.; Data Acquisition- Z.A., C.C.; Data Analysis/Interpretation- Z.A., H.A., M.T., İ.H.B.; Drafting Manuscript- Z.A., C.C., İ.H.B.; Critical Revision of Manuscript- Z.A., H.A., M.T.; Final Approval and Accountability- Z.A., H.A., C.C., İ.H.B., M.T.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

Etik Komite Onayı: Çalışma protokolü Yerel Etik Kurul tarafından onaylandı (Protokol Numarası: 2015/ 09-2) ve Helsinki Bildirgesi'ne uygun olarak yapıldı.

Bilgilendirilmiş Onam: Katılımcılardan bilgilendirilmiş onam alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Çalışma Konsepti/Tasarım- Z.A., H.A., M.T.; Veri Toplama- Z.A., C.C.; Veri Analizi/Yorumlama- Z.A., H.A., M.T., İ.H.B.; Yazı Taslağı- Z.A., C.C., İ.H.B.; İçeriğin Eleştirel İncelemesi- Z.A., H.A., M.T.; Son Onay ve Sorumluluk- Z.A., H.A., C.C., İ.H.B., M.T.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

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