New Index for the Discrimination of Acute Streptococcal Tonsillopharyngitis and Infectious Mononucleosis: Infection Discrimination Index

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Abstract

Objective: This study aimed to discriminate group A β-hemolytic streptococcus (GABHS) and Epstein-Barr virus (EBV) that cause acute tonsillopharyngitis with a new index called the infection discrimination index (IDI).

Material and Methods: Based on the throat culture and viral capsid Ag Ig M results, 110 GABHS-positive children and 52 EBV-positive children were enrolled in the GABHS and EBV groups, respectively. Fifty children who had undergone a medical examination at the pediatric clinic comprised the control group. The IDI means of the three groups (GABHS, EBV, control) were subjected to a statistical comparison.

Results: The groups did not significantly differ in terms of sex and age (p: 0.453 and 0.662, respectively). The IDI means of the three groups were significantly different (p<0.001). Receiver operating characteristic (ROC) analysis was performed to calculate the sensitivity and specificity of IDI in the GABHS and EBV groups. The ROC analysis demonstrated a sensitivity of 68.2% and specificity of 92% for predicting GABHS infection. The sensitivity and specificity was 53.8% and 96%, respectively, for predicting EBV infection.

Conclusion: IDI calculated from the data of complete blood count can serve as a biomarker for discriminating between GABHS and EBV infections. We believe that the findings of this study would be particularly helpful for centers where throat culture and/or antibody tests cannot be performed. It is a rapid, practical, noninvasive, and cost-effective index.

Keywords: Tonsillitis, pharyngitis, infectious mononucleosis, streptococcus pyogenes, Epstein-Barr virus infections, index

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INTRODUCTION

Acute tonsillopharyngitis (AT) is a common cause of sore throat that often results from viral infections (1). Common viral agents of AT include adenovirus, rhinovirus, coronavirus, respiratory syncytial virus, and Epstein-Barr virus (EBV) (2, 3). Among the bacterial agents, Group A β-hemolytic streptococcus (GABHS) is the most commonly encountered pathogen (1).

The incidence of AT attributable to GABHS in children is between 15% and 30% (4-6). In general, the symptoms of GABHS infection are sore throat, fever, malaise, myalgia, and headache (7). When AT is believed to be caused by a viral agent, symptomatic treatment is administered; when GABHS is suspected, antibiotherapy should be initiated. Life-threatening complications, such as acute rheumatic fever, poststreptococcal glomerulonephritis, and bacteremia caused by GABHS, need to be prevented (1).

EBV of the Herpesviridae family infects 90%-95% of the adult population across the world (8). In contrast, the seroprevalence ratio of EBV among children is low. In the United States of America, the general seroprevalence of EBV in children aged 6-19 y is 66.5% (9). About 25%-30% of primary infections in adolescents and adults cause infectious mononucleosis (IM) that is characterized by fever, lymphadenopathy, and AT (3). IM is usually a self-limiting illness that rarely has serious complications, such as meningoencephalitis, myocarditis, pericarditis, pancreatitis, and splenic rupture (10); however, IM can be fatal.

This study aimed to discriminate GABHS from EBV that cause AT, using a new index called the infection discrimination index (IDI).

MATERIAL AND METHODS

Patient Selection

This study was performed in our tertiary clinic from January 2019 to March 2020. The ethical committee of the institution approved our study protocol (Clinical Research Ethics Committee of Süleyman Demirel University School of Medicine; Approval Date: April 4, 2020; Approval Number: 115), and the study was performed as per the principles in the Helsinki Declaration. The study was designed as a retrospective study; therefore, informed consent was not obtained from the subjects. Patients with AT were included in the study as per the following inclusion criteria: 1) age 5-15 y, 2) presence of clinical findings of AT (fever, sore throat and tonsillopharyngeal hyperemia, exudate, and edema), 3) complete blood count (CBC) test, 4) GABHS-positive result on throat culture or EBV Viral Capsid Ag (VCA) IgM positivity on blood test, and 5) no medications (antibiotics, anti-inflammatory, etc.). The exclusion criteria were as follows: 1) autoimmune diseases (e.g., type 1 diabetes mellitus, autoimmune thyroid diseases), 2) chronic infectious diseases (e.g., tuberculosis, brucella), 3) chronic systemic inflammatory diseases (e.g., acute or chronic renal insufficiency, chronic liver disease, connective tissue disease, inflammatory bowel disease, or cardiac disorders), 4) obesity, 5) use of drugs likely to increase the serum neutrophil or leukocyte count, 6) systemic steroid use, 7) hematologic disorders, and 8) malignancy.

The patients who met the inclusion criteria were divided into two groups, the GABHS group and the EBV groups. Children aged 5-15 y who had undergone a medical examination at a pediatric clinic, did not have any history of chronic diseases or acute infections within the previous month, and were not on any medication for the previous 3 month comprised the control group. All of the patients who were fasting for 8 h and whose CBC tests were performed between 6 AM and 10 AM were enrolled. The IDI

$$\left(\frac{The\ Number\ of\ neutrophil\ (10^3/\mu L)}{The\ Number\ of\ lymphocyte\ (10^3/\mu L) + The\ Number\ of\ monocyte\ (10^3/\mu L)}\right)$$

means of the 3 groups (GABHS, EBV, and control) were calculated and compared statistically.

Statistical Analysis

Data were analyzed using IBM Statistical Package for the Social Sciences version 24.0 (IBM SPSS Corp.; Armonk, NY, USA). With respect to descriptive findings, while the categorical variables are presented as percentages, continuous variables are presented as mean±standard deviation values. Chi-square test was performed based on sex to determine the relationships among the groups. Parametric tests were performed in order to compare the means of the continuous variables between the groups because the number of children in each group was ≥30. One-way ANOVA was performed to evaluate the difference among the mean IDIs of the groups. A p value <0.05 was considered to indicate statistical significance. The ability of the IDI value to predict the presence of GABHS and EBV infections was analyzed using receiver operating characteristics (ROC) curve analysis. When a significant cut-off value was observed, the sensitivity and specificity values were presented.

RESULTS

Between January 2019 and March 2020, 219 patients were admitted to our clinic with AT symptoms. Fifty-seven of the 219 patients were excluded from the study because they did not fulfill the inclusion criteria. The GABHS, EBV, and control groups included 110, 52, and 50 patients, respectively. We found that the GABHS group included 57 (51.8%) men and 53 (48.2%) women; the EBV group included 27 (51.9%) men and 25 (48.1%) women; the control group included 31 (62%) men and 19 (38%) women. The average ages were 104.05±34.38 mon, 109.00±38.98 mon, and 103.88±29.13 mon in the GABHS, EBV, and control groups, respectively. The groups did not differ significantly in terms of sex and age (p: 0.453 and 0.662, respectively) (Table 1).

The average neutrophil count, lymphocyte count, monocyte count, and IDI was 8.18±4.79 (10^3/μL), 2.13±1.62 (10^3/μL), 0.87±0.38 (10^3/μL), and 3.17±2.17, respectively, in the GABHS group; 3.81±2.01 (10^3/μL), 6.32±4.14 (10^3/μL), 1.00±0.69 (10^3/μL), and 0.78±0.73, respectively in the EBV group; and 3.83±1.25 (10^3/μL), 2.71±0.77 (10^3/μL), 0.57±0.14 (10^3/μL), and 1.22±0.48, respectively in the control group. The average IDI of the three groups was significantly different (p<0.001) (Table 2).

ROC analysis showed that IDI possesses diagnostic value for predicting GABHS infection [area under curve (AUC): 0.821, 95% confidence interval (CI): 0.758-0.884, p<0.001]. On the basis of the analysis, the optimum cut-off value was determined as 1.85. With this cut-off value, the sensitivity and specificity of the IDI was 68.2% and 92% for predicting GABHS infection. Moreover, IDI had diagnostic value for predicting EBV infection (AUC: 0.759, 95% CI: 0.662-0.856, p<0.001). As per the analysis, the optimum cut-off value was determined as 0.62. With this cut-off value, the sensitivity and specificity of the IDI was 53.8% and 96%, respectively, for predicting EBV infection (Figure 1 and 2).

Table 1. Demographic characteristics of the groups and p values

	Patient Group (n: 162)		Control (n: 50)	p[a]
	GABHS (n: 110)	EBV (n: 52)		
Sex				
Male	57 (51.8%)	27 (51.9%)	31 (62%)	0.453
Female	53 (48.2%)	25 (48.1%)	19 (38%)	
Age (month)				
mean±sd	104.05±34.38	109.00±38.98	103.88±29.13	0.662
Min.	60	61	60	
Max.	180	180	168	

[a]p<0.05 was accepted as significant
GABHS: group A β-hemolytic streptococcus; EBV: Epstein-Barr virus; sd: standard deviation; Min: minimum; Max: maximum

Table 2. The average neutrophil count, lymphocyte count, monocyte count, and IDI for the groups and p value

CBC parameters (mean±sd)	Patient Group (n: 162)		Control (n: 50)	p[a]
	GABHS (n: 110)	EBV (n: 52)		
Neutrophil count (10^3/μL)	8.18±4.79	3.81±2.01	3.83±1.25	<0.001
Lymphocyte count (10^3/μL)	2.13±1.62	6.32±4.14	2.71±0.77	<0.001
Monocyte count (10^3/μL)	0.87±0.38	1.00±0.69	0.57±0.14	<0.001
IDI	3.17±2.17	0.78±0.73	1.22±0.48	<0.001

[a]p<0.05 was accepted as significant
CBC: complete blood count; GABHS: group A β-hemolytic streptococcus; EBV: Epstein-Barr virus; IDI: infection discrimination index

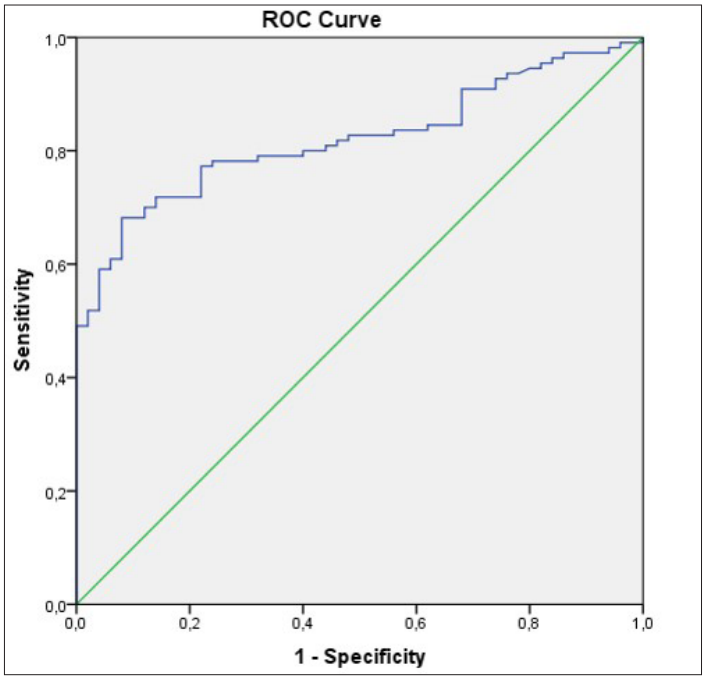

Figure 1. ROC curve analysis of the IDI value for the GABHS group (Cut-off value 1.85)
ROC: receiver operating characteristics; IDI: infection discrimination index; GABHS: Group A β-hemolytic streptococcus

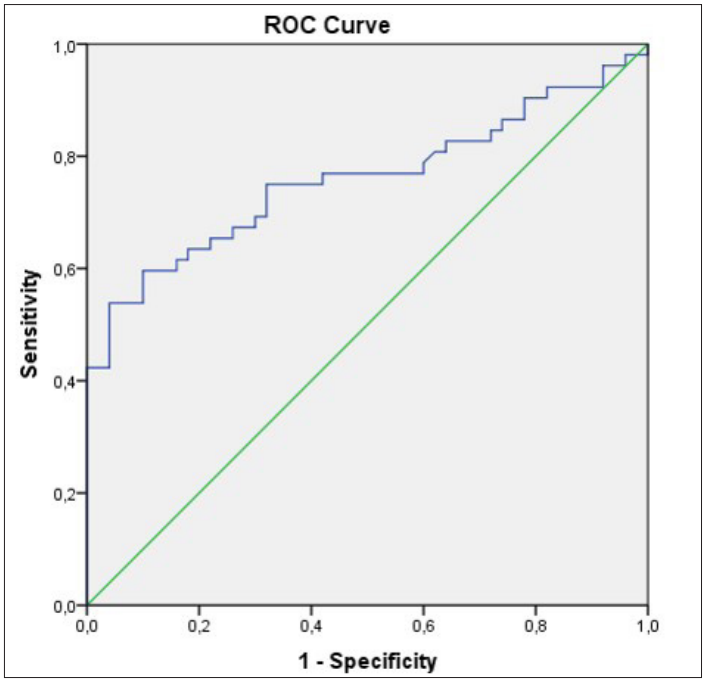

Figure 2. ROC curve analysis of the IDI value for the EBV group (Cut-off value 0.62)
ROC: receiver operating characteristics; IDI: infection discrimination index; EBV: Epstein-Barr virus

DISCUSSION

Several indexes, biomarkers, and formulations can be used as CBC parameters that support the diagnosis or extrapolate disease prognosis. The main parameters are the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and systemic immune inflammatory index. Several studies support new indexes and biomarkers (11). Thus, we recommended the use of a new index called the IDI for distinguishing between viral and bacterial AT agents. To our knowledge, this index has not been previously defined in the literature.

Lymphopenia, accompanying neutrophilia, is usually a good predictor of bacteremia (12). Thus, neutrophils are the most involved leukocyte subtype in bacterial infections and explain neutrophil-induced leukocytosis in GABHS infections. In the present study, the average neutrophil value of the GABHS group was higher than that of the EBV group and control group. Leukocytosis and lymphocytosis are common EBV-associated laboratory findings (13). Some studies have shown that an elevated lymphocyte count is specific to EBV infection, and the use of the lymphocyte/leucocyte ratio is recommended for performing the differential diagnosis (14, 15). Çağlar et al. (16) found an increased lymphocyte/leucocyte ratio (>50%) in 57.5% of patients with IM. In the present study, the mean lymphocyte of the EBV group was higher than that in the GABHS group and control group. The present results are compatible with those reported in the literature, indicating the importance of lymphocytosis in IM. Monocytosis is characterized by an increased monocyte count in CBC. Bicer et al. (17) detected 66.5% of various viral pathogens in patients with respiratory infections and reported monocytosis as the most remarkable laboratory finding in viral infections. In the present study, the mean monocyte value of the EBV group was higher than the value in the GABHS group and control group.

IDI is calculated using the neutrophil/lymphocyte+monocyte formula. Changes in the CBC with respect to infections enabled us to establish the hypothesis that the IDI is higher in GABHS infections than in IM. Therefore, we speculated that IDI might be an alternative to other tests for diagnosing AT.

Rapid antigen testing is widely used for GABHS diagnosis. One disadvantage of this test is that it cannot distinguish GABHS carriers. In children, the reported sensitivity of rapid antigen tests is about 85%; however, the sensitivity varies considerably among studies, ranging from 66% to 99%, and the specificity is high and stable, at about 95% (18-20). IDI is expected to be a possible biomarker with diagnostic value in predicting AT caused by GABHS. In the present study, IDI had a sensitivity of 68% and specificity of 92% at optimum cut-off value. Although the sensitivity of IDI is relatively low, it is similar to the sensitivity of the rapid antigen test in some studies (18). Also, the specificity of IDI is similar to rapid antigen test (20).

Throat culture is used as the gold standard method for diagnosing streptococcal AT (21). The major advantage of laboratory throat culture is its detection of GABHS from swabs even in the presence of very few bacteria; however, the 48-hour delay in the results is a major limitation of this method because the disease may progress during these 48 h (22). Early diagnosis and treatment are crucial. Delayed treatment increases the risk of development of suppurative (cervical lymphadenitis, retropharyngeal abscess, peritonsillar cellulitis or abscess) and nonsuppurative (acute rheumatic fever, rheumatic heart disease and acute glomerulonephritis) complications associated with GABHS (23, 24). Another disadvantage of throat culture is that (similar to rapid antigen test) it cannot distinguish GABHS carriers from those who have had viral AT (22). About 10%-15% of healthy pediatric subjects are GABHS carriers (25). Therefore, false positivity may lead to the unnecessary use of antibiotics, exposure to antibiotics-related adverse effects, and increased treatment cost. IDI is a good alternative to antibiotic treatment in clinics where GABHS infection is considered but throat culture and rapid antigen test cannot be performed.

IM is a disease caused by EBV and is especially common in adolescents and children. Typical signs and symptoms of IM include fever, pharyngitis, adenopathy, malaise, and atypical lymphocytosis (26), most of which are similar to other AT agents. Diagnostic tests should be performed as early as possible to decide whether antibiotics treatment should be initiated. Increased lymphocyte count in CBC is an expected laboratory finding in IM. Brigden et al. (27) found lymphocytosis (at least >50% lymphocytes in the CBC) in 120 of 180 patients with positive heterophile antibodies. The IDI value is expected to be low with lymphomonocytosis in IM. In the present study, the mean IDI of the EBV group was lower than that of the control group and GABHS group. If patients with suspected IM have a low IDI, we recommend symptomatic therapy under close supervision.

In a study wherein the heterophile antibody test used for IM diagnosis was compared in nine different kits, the sensitivity was 25%-50% in patients aged <12 y and 71%-91% in those aged >12 y (28). The heterophile antibody test is not recommended for use in pediatric patients, particularly those aged <12 y because of the high rates of false negative or false positive results (13). In the present study, the patient group was aged 5-15 y. The IDI had 53% sensitivity and 96% specificity at the optimum cut-off value in patients of this age group. Thus, in younger age groups, IDI may be more useful than heterophile antibody tests. In future studies, the calculation of the IDI in age and sex subgroups may provide favorable values of the sensitivity and specificity ratios. The most sensitive tests for IM diagnosis are EBV-specific serology tests (EBV VCA IgM, EBV EA antibodies) (29). However, the cost and absence of these tests in some clinics are limitations for its use. We included only EBV VCA IgM antibody positive patients in the EBV group for standardization.

However, our study has certain limitations. First, this was a single-center, retrospective case analysis, and causality was difficult to confirm. Second, we only recorded the IDI at admission; however, monitoring of the dynamic IDI changes after treatment could also be useful. Third, the number of patients in the EBV group was smaller than that in the GABHS group. Therefore, the sensitivity rate of the EBV group may be affected. Finally, we could only compare the IDIs of the GABHS and EBV agents because the number of other AT agents was inadequate for performing the study. We recommend that in the future, studies on a larger sample be performed by calculating the IDI in AT caused by other agents (e.g., Gram+, Gram- bacteria and CMV, rhinovirus, RSV, influenza virus, and coronavirus).

CONCLUSION

The IDI calculated from the data of CBC can serve as a biomarker for distinguishing between GABHS and EBV. In centers where throat culture and/or antibody tests cannot be performed, IDI can contribute toward the discrimination of GABHS from EBV infections. The optimum cut-off values of IDI should be considered for an accurate diagnosis, and IDI should always be interpreted in context to the patient's complaints and clinical findings.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of Süleyman Demirel University School of Medicine (Approval Date: April 4, 2020; Approval Number: 115).

Informed Consent: Informed consent was not obtained due to the nature of the study.

Peer-review: Externally peer-reviewed.

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