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Is it possible to predict appendicitis caused by *Enterobius vermicularis* before surgery?

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Abstract

Objectives: This study aimed to develop statistical models based on hemogram data to predict the presence of the nematode parasite *Enterobius vermicularis* (EV) in the appendix before surgery.

Patients and methods: The retrospective case-control study was generated from histopathological data of appendectomy 9,605 patients between January 1, 2007, and August 1, 2023. *Enterobius vermicularis* was detected in 32 patients (24 pediatric and 8 adult patients). Six patients were excluded due to missing hemograms, and 26 participants (pediatric patients: 10 males, 9 females; mean age: 11.1±4.4 years; range, 2 to 17 years & adult patients: 1 male, 6 females; mean age: 39.9±14.7 years; range, 22 to 68 years) were evaluated. The control (non-EV) group was composed of 99 randomly selected patients (42 males, 57 females; mean age: 18.3±13.5 years; range, 2 to 68 years) of nonparasitic acute appendicitis with available preoperative hemogram data. Univariate analysis was conducted on hemogram parameters to compare the groups, followed by predictive modeling using binomial logistic regression.

Results: *Enterobius vermicularis* was present in 0.33% of all appendicitis patients and in 0.54% of pediatric patients. Histopathological diagnosis of appendicitis was present in 46.8% of EV patients, with a higher rate among pediatric patients (50%) compared to adult patients (37.5%). Patients with EV exhibited significantly lower counts of neutrophils and white blood cells in comparison to the non-EV group (p-values 0.031 and 0.046, respectively). The most effective EV prediction model (area under the curve: 0.685 [0.528-0.770]) ultimately included platelet distribution width and neutrophil count after evaluating all parameters (with corresponding p-values of 0.022 and 0.042, respectively).

Conclusion: It is difficult to predict the presence of EV based on hemogram data prior to appendectomy. Studies that collect large amounts of data from multiple centers and different populations could provide better predictive models.

Keywords: Acute appendicitis, *Enterobius vermicularis*, hemogram, neutrophil, white blood cell.

Acute appendicitis (AA) is the most common abdominal surgical emergency worldwide, with an estimated incidence of 233 patients per 100,000 population in a year.[1] Appendicitis is caused by the inflammation of the appendix, which can be caused by a variety of factors, including infection, blockage, or trauma. If appendicitis is not treated promptly, it can lead to severe complications, such as peritonitis (inflammation of the lining of the abdomen), sepsis (a life-threatening infection), and even death.[2] Therefore, rapid diagnosis and treatment of AA is essential to avoid the significant morbidity and mortality associated with appendiceal perforation.[3] Despite advances in diagnostic imaging and clinical scoring systems, the timely diagnosis of AA remains challenging for most practitioners, particularly before the onset of complications.[4] Appendectomy, performed either through open laparotomy or laparoscopy, is the definitive treatment for AA.[5]

The nematode parasite *Enterobius vermicularis* (EV), a pinworm, causes enterobiasis (pinworm infestation) in humans. Enterobiasis is common globally, affecting both temperate and tropical climates, with an estimated 1 billion people infected.[6] Adults are also at risk of enterobiasis, although it mainly affects the pediatric population. Schoolchildren living in crowded and unsanitary conditions are the most susceptible to infestation.[7,8] Diagnosis of enterobiasis

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is based on clinical presentation or microscopic identification of pinworm eggs due to the lack of specific stool or serological tests.

It is difficult to diagnose enterobiasis at the initial diagnosis of appendicitis due to the emergent nature of the disease. The first six patients of EV detected in the appendix were reported in 1899.[9] Despite many studies assessing the link between EV and appendicitis, the association has not been clearly established.[10-14] Therefore, this study aimed to develop statistical models based on laboratory data to predict the presence of the parasite in the appendix before the surgery.

PATIENTS AND METHODS

Data on histopathological examination results for all patients (n=9,605) of appendectomy were obtained from the information system of the Göztepe Prof. Dr. Süleyman Yalçın City Hospital between January 1, 2007, and August 1, 2023. Thirty-two patients (24 pediatric and eight adult patients) with EV detected by histopathological examination were identified. Their hemogram data at the first hospital admission were then collected from the hospital information system. There were six patients without laboratory data due to exchange in software systems during this long period, and these patients were excluded, yielding 26 participants (pediatric patients: 10 males, 9 females; mean age: 11.1±4.4 years; range, 2 to 17 years & adult patients: 1 male, 6 females; mean age: 39.9±14.7 years; range, 22 to 68 years) for the final analysis, with 19 pediatric and seven adult patients included in the study as the EV group. Ninety-nine randomly selected patients (42 males, 57 females; mean age: 18.3±13.5 years; range, 2 to 68 years) with available laboratory data and no parasite detected by histopathological examination were used as controls (non-EV group). Controls were selected from the non-EV group of approximately the same age and sex as the EV patients at both stages. The flow diagram of the study is illustrated in Figure 1.

After obtaining data from the hospital information system, the previously stained slides with EV detected were retrieved from the archive, and all slides were examined under a microscope for the presence of EV. The slides had been stained with hematoxylin and eosin previously. The presence of the parasite was confirmed before the statistical analysis.

Hemogram parameter values of the patients and the controls were obtained from the hospital information system. White blood cell count (WBC), lymphocyte count, neutrophil count, monocyte count, eosinophil count, platelet count, mean platelet volume, platelet

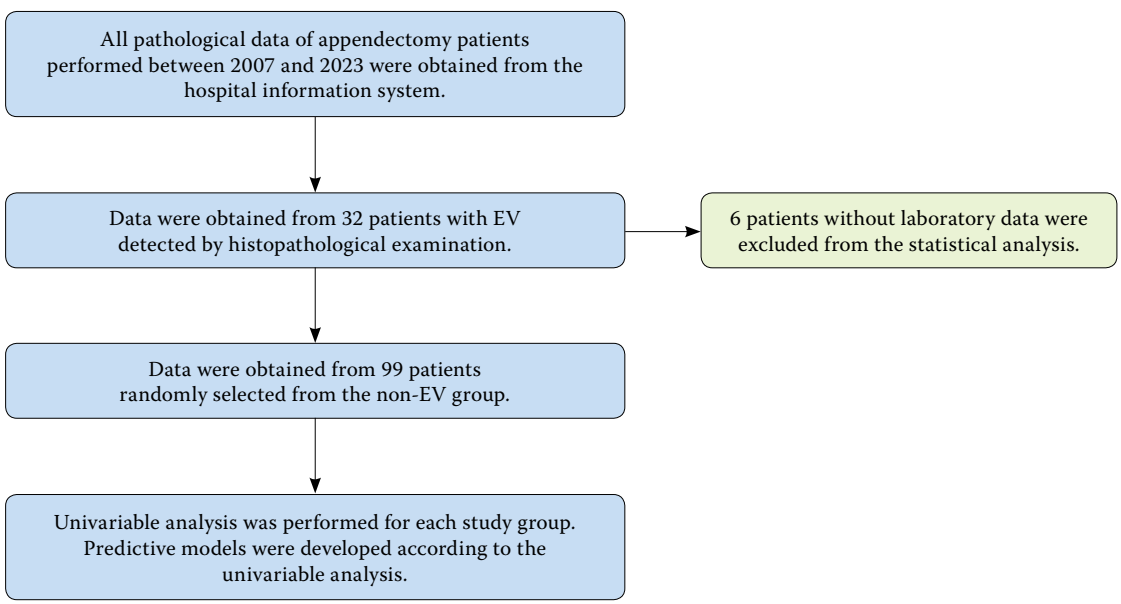

Figure 1. Flowchart of the study.
EV: *Enterobius vermicularis*.

distribution width (PDW) values, two known indexes (systemic inflammatory index [SII] and systemic inflammatory response index [SIRI]), and different formulas generated from these parameters were used for statistical analysis. These formulas were as follows: LxM (lymphocyte count multiplied by monocyte count), LxMxN (lymphocyte multiplied by monocyte count multiplied by neutrophil count), MLR (monocyte to lymphocyte ratio), MxN (monocyte multiplied by neutrophil count), NLR (neutrophil to lymphocyte ratio). The formulas of SII and SIRI were neutrophil × platelet/lymphocyte count, and neutrophil × monocyte/lymphocyte count, respectively. C-reactive protein (CRP) was excluded due to incomplete data in some patients.

Statistical analysis

Statistical analyses were performed with Jamovi version 2.4.5 (www.jamovi.org). After obtaining all the data in a Microsoft Excel (Microsoft Corp., Redmond, WA, USA) file, the frequencies of patients EV detected in histopathological examination were determined (descriptive analysis). Then, with the presence of disease as the dependent variable, the Mann-Whitney U test was used to determine the effect of each parameter, and the significance of the differences was found (univariate analysis). Univariable analyses were performed for each study group in both stages of the study. A p-value <0.05 was considered significant, binomial (bivariate) logistic regression was performed with the parameters significant for their role in disease detection, and the models were tested. Models with the highest area under the curve on the receiver operating characteristic (ROC) curve were identified and their sensitivity and specificity were calculated (predictive analysis). Predictive analysis was based on logistic regression to obtain a probability for each individual to belong to the EV group. The ROC curve was plotted to show the different decision thresholds.

RESULTS

The findings indicated that EV was present in 32 (0.33%) of 9,605 patients of appendicitis and 24 (0.54%) of 4,407 pediatric patients. Figure 2 displays the images of the parasites found in the

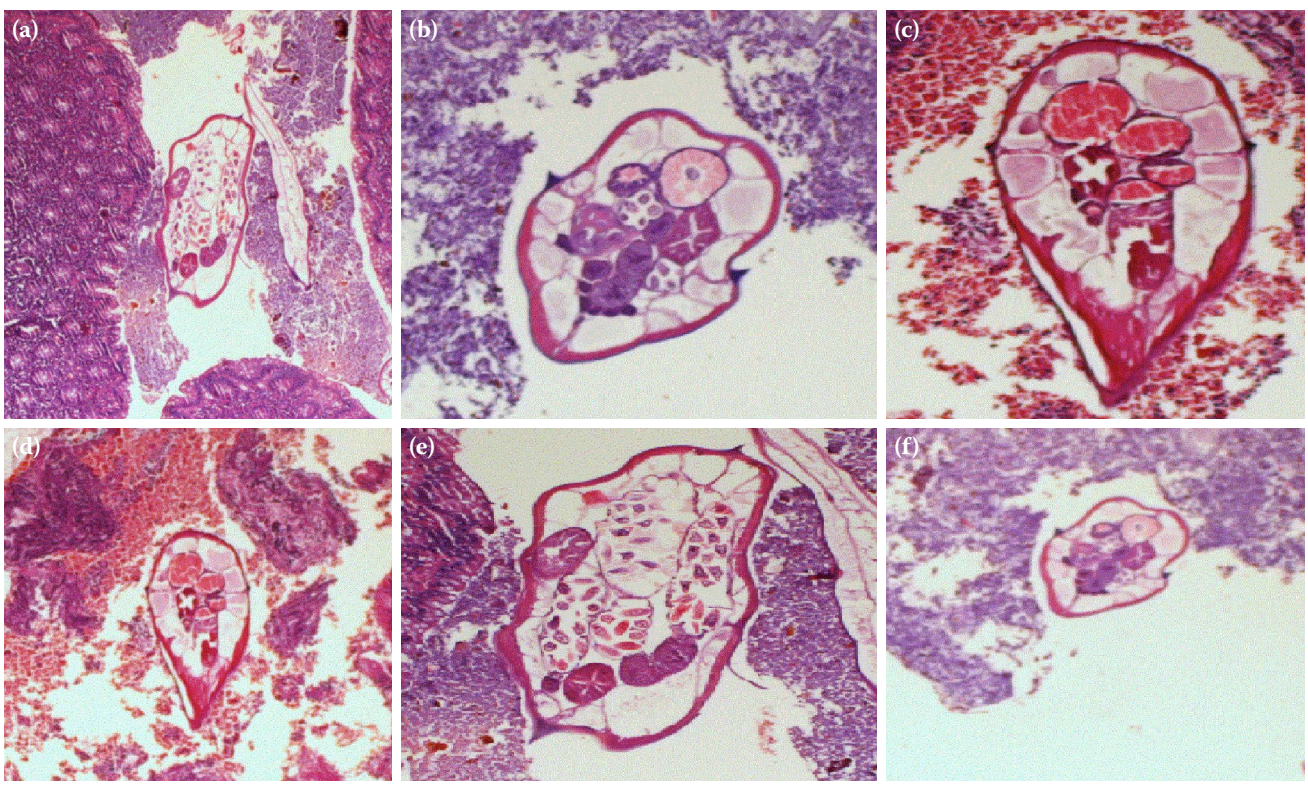

Figure 2. Images of the parasites detected in the histopathological examination of slides stained with hematoxylin and eosin (H&E, **(a)** ×100, **(b)** ×200, **(c)** ×200, **(d)** ×100, **(e)** ×200 and **(f)** ×100 magnification from top left to bottom right).

appendix vermiformis. Table 1 demonstrates the clinicopathological and demographic characteristics of all 32 patients with EV detected in histopathological examination of appendix vermiformis. Clinical diagnosis and laboratory data are missing for 11 and 6 patients, respectively, due to a change in the hospital information system over the past 10 years. Most of the patients presented to the hospital with abdominal pain and had a diagnosis of acute abdomen' prior to surgery. There

TABLE 1

Clinicopathological and demographic characteristics of patients with EV detected in histopathological examination of appendix vermiformis

Patients no	Age/Sex	Preoperative diagnosis	Postoperative diagnosis	Pathological appendicitis (n/n=15/32)	Lymphoid hyperplasia (n/n=22/32)	White blood cell count	Neutrophil count
1	2/F	Intussusception	Acute app.	No	Yes	14.5	9
2	5/M	Acute abdomen	Bezoar	No	Yes	12.3	7.54
3	6/F	Acute abdomen	Acute app.	No	Yes	19.6	15.5
4	7/M	Acute abdomen	Acute app.	**Yes**	Yes	15.5	12.19
5	8/F	Acute abdomen	Acute app.	**Yes**	Yes	14.7	12.3
6	9/M	Acute abdomen	Acute app.	**Yes**	No	8.6	7.23
7	9/M	Acute abdomen	Acute app.	**Yes**	Yes	11.1	6.73
8	10/F	Acute abdomen	Acute app.	No	Yes	8.9	7.24
9	11/M	Acute app.	Acute app.	No	Yes	15.4	10.9
10	11/F	Acute abdomen	Acute app.	No	Yes	6.8	3.17
11	11/F	Acute abdomen	Acute app.	No	Yes	13.3	6.66
12	11/M	Acute abdomen	Acute app.	**Yes**	Yes	10.1	8.27
13	12/F	Missing	Missing	No	Yes	Missing	Missing
14	12/M	Missing	Missing	**Yes**	No	Missing	Missing
15	12/F	Missing	Missing	No	Yes	Missing	Missing
16	14/F	Missing	Missing	No	Yes	Missing	Missing
17	15/M	Acute abdomen	Acute app.	**Yes**	Yes	17.06	12.56
18	15/M	Acute abdomen	Acute app.	**Yes**	Yes	14	12.34
19	15/F	Missing	Missing	**Yes**	No	12.9	12
20	16/F	Acute abdomen	Acute app.	No	Yes	8.1	6.3
21	16/M	Missing	Missing	**Yes**	No	8.9	6.19
22	17/M	Acute abdomen	Acute app.	**Yes**	Yes	14.22	11.32
23	17/F	Missing	Missing	No	Yes	11.2	8.61
24	17/M	Missing	Missing	**Yes**	No	Missing	Missing
25	18/F	Missing	Missing	**Yes**	No	Missing	Missing
26	22/M	Acute app.	Acute app.	**Yes**	Yes	12.7	9.27
27	30/F	Missing	Missing	No	Yes	7.8	4.68
28	35/F	Acute app.	Acute app.	No	No	17	15.5
29	36/F	Acute app.	Acute app.	No	Yes	14.1	8.91
30	41/F	Acute app.	Acute app.	No	No	10.1	6.45
31	47/F	Missing	Missing	**Yes**	No	13.75	11.21
32	68/F	Over cancer	Cancer+ Acute app.	No	No	7.3	5.15

EV: *Enterobius vermicularis.*

were pathological findings of AA in all of the patients except for two adult patients (Patients 28 and 32). Although Patient 28 was admitted with abdominal pain and had a high WBC, the pathological findings did not support the diagnosis. Patient 32 had major cancer surgery with normal WBC level, indicating that the presence of EV was likely incidental. Fifteen (46.8%) out of 32 patients with EV had a histopathological diagnosis of appendicitis (12 out of 24 pediatric patients, 50%; three out of eight adult patients, 37.5%).

Significantly lower neutrophil and WBC counts were found in patients with EV compared to the non-EV group. Although some other inflammatory parameters (L×M×N, MLR, M×N, monocyte count, NMR, NLR, SII, and SIRI) were lower in EV patients, the differences were not significant. There were no

TABLE 2
Univariable analysis of all parameters between two groups

	Non-EV group (n=99)					EV* group (n=26)					
Parameters	n	%	Mean±SD	Median	25^{th}-75^{th} percentile	n	%	Mean±SD	Median	25^{th}-75^{th} percentile	*p*
Age				14.0	11.0-17.0				15.0	9.25-20.8	0.86
Basophil				0.0400	0.0200-0.0800				0.0200	0.0125-0.0500	0.11
E/M				0.0916	0.0174-0.1990				0.1430	0.0253-0.3480	0.19
E/N				0.00775	0.00110-0.01500				0.01210	0.00326-0.02780	0.19
EO				0.060	0.010-0.155				0.100	0.030-0.217	0.36
HCT				39.0	36.0-41.5				38.0	37.0-41.0	0.97
HGB				13.1	11.9-13.9				12.9	12.3-13.6	0.95
L×M				1.43	0.80-2.42				1.49	0.69-2.34	0.83
L×M×N				15.6	7.91-27.9				13.3	4.91-25.4	0.29
LYM				1.90	1.30-2.70				2.15	1.37-2.90	0.64
MLR				0.408	0.261-0.604				0.355	0.226-0.570	0.28
M×N				8.47	5.21-11.9				7.04	4.09-9.01	0.076
MON				0.770	0.570-1.000				0.690	0.570-0.987	0.52
MPV				8.70	6.70-10.4				8.20	6.50-9.25	0.14
NMR				13.5	10.5-17.3				11.4	9.26-16.6	0.29
NEU				11.1	7.92-13.8				8.76	6.68-11.8	**0.031**
NLR				5.58	2.86-10.5				4.59	2.30-6.92	0.21
PDW				16.4	16.1-17.1				16.3	15.7-16.8	0.074
PLT				283	226-325				266	218-329	0.94
SII				1551	943-2793				1341	720-2124	0.22
SIRI				4.49	2.41-7.68				3.52	1.68-4.96	0.071
WBC				14.3	10.9-16.9				12.8	9.20-14.4	**0.046**
MCV			83.3±4.78					83.6±5.94			0.83
Sex Female Male	 57 42	 58 42				 15 11	 58 42				 0.99 -

EV: *Enterobious vermicularis*; IQR: Interquartile range; E/M: Eosinophil/monocyte count; E/N: Eosinophil/neutrophil count; EO: Eosinophil count; HTC: Hematocrit; HGB: Hemoglobin; L×M: Lymphocyte multiply monocyte count; L×M×N: Lymphocyte multiply Monocyte multiply Neutrophil count; LYM: Lymphocyte count; MLR: Monocyte to lymphocyte ratio; M×N: Monocyte multiply neutrophil count; MON: Monocyte count; MPV: Mean platelet volume; NMR: Neutrophil to monocyte ratio; NEU: Neutrophil count; NLR: Neutrophil to lymphocyte ratio; PDW: Platelet distribution width; PLT: Platelet count; SII: Systemic inflammatory index; SIRI: Systemic inflammatory response index; WBC: White blood cell count; MCV: Mean corpuscular volume.

TABLE 3
Model coefficients to predict EV

		95% CI						95% CI	
Predictor	Estimate*	Lower	Upper	SE**	Z	*p*	Odds ratio	Lower	Upper
Intercept	10.193	1.274	19.11148	4.5505	2.24	0.025	26708.334	3.575	2.00e+8
PDW	-0.630	-1.171	-0.08944	0.2760	-2.28	0.022	0.532	0.310	0.914
Neutrophil count	-0.118	-0.231	-0.00424	0.0580	-2.03	0.042	0.889	0.793	0.996

EV: *Enterobius vermicularis*; CI: Confidence interval; * Estimates represent the logarithm of the odds ratio between the EV group and the Non-EV group; **: Standard error; PDW: Platelet distribution width.

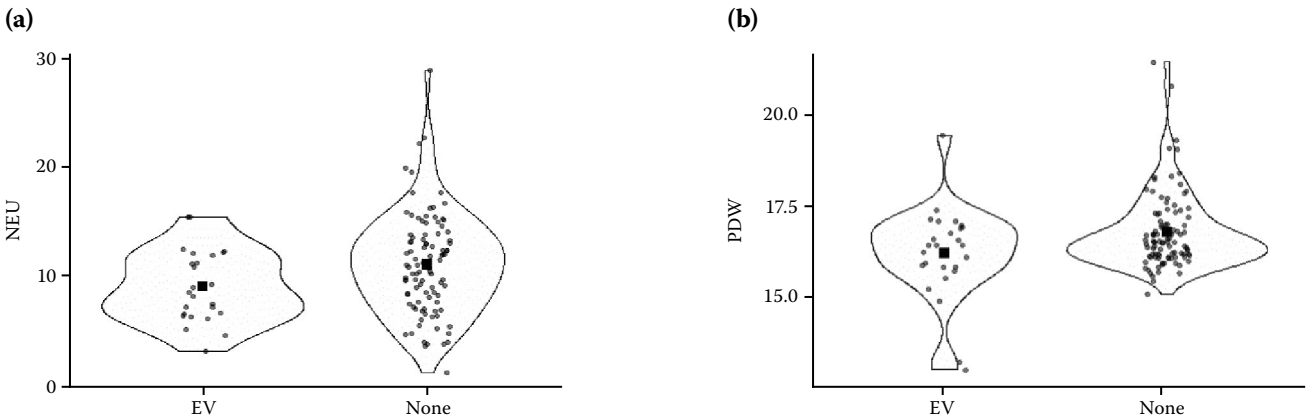

Figure 3. Data distribution of **(a)** neutrophil (NEU) count and **(b)** Platelet distribution width (PDW).
EV: *Enterobius vermicularis*.

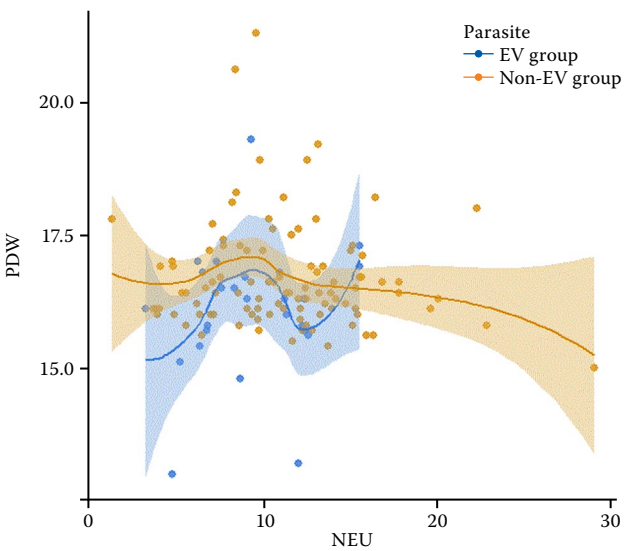

Figure 4. Scatter plot of PDW and neutrophil count with standard deviations.
EV: Enterobius vermicularis; NEU: Neutrophil; PDW: Platelet distribution width.

significant differences in demographic parameters (age and sex) between the groups (p=0.86 and p=0.99, respectively). The number of eosinophils was slightly higher in the EV group, but the difference was not significant (p=0.36). Hemoglobin, hematocrit, mean platelet volume, PDW, and platelet levels were also slightly and insignificantly lower in the EV group (Table 2). After obtaining these univariable results, we performed predictive binomial multiple logistic regression analyses with different parameters. Adjusting neutrophils and WBC as a predictive model did not give the best result. Therefore, we also tested other insignificant parameters. The best model eventually included PDW and neutrophil after testing all parameters (p-values in the model were 0.022 and 0.042, respectively). Platelet distribution width had a higher Z-score than neutrophil count (Table 3). Figures 3 and 4 highlight the data distribution and scatter plot of PDW and neutrophil values of the groups, respectively. The ROC curves of PDW, neutrophils, and the best model to identify possible

TABLE 4
Possible reference cut-off values to detect EV patients for the parameters in the best model

Parameter	Reference cut-off	Sensitivity%	Specificity%	AUC	95% CI
Neutrophil count	≤8.91	68.7	50.0	0.638	0.549-0.724
Neutrophil count	≤9.27	65.7	57.7	0.638	0.549-0.724
Neutrophil count	≤10.9	51.5	61.5	0.638	0.549-0.724
PDW	≤16.3	60.6	46.2	0.614	0.525-0.702
PDW	≤16.5	46.5	57.7	0.614	0.525-0.702

EV: *Enterobius vermicularis*; AUC: Area under curve; CI: Confidence interval; PDW: Platelet distribution width.

cut-off values for detecting EV patients were extracted. Table 4 and Figure 5 show the possible cut-off values with the sensitivity and specificity rates and the ROC curve of the best model, respectively.

DISCUSSION

The main finding of this study was the effect of PDW and neutrophil count in predicting the presence of EV in the appendix vermiformis prior to appendectomy. Neutrophil parameters and indices have been investigated in various studies on appendicitis. Zachos et al.[15] found the best model, including the pediatric appendicitis score, neutrophil percentage, and CRP, to predict the risk of complicated appendicitis in children. Corkum et al.[16] found that an absolute neutrophil count over 8,000/mm^3 may be an indication that further imaging is required in suspected patients of appendicitis. Therefore, the neutrophil count is significant in diagnosing appendicitis. Nonetheless, the precise function of neutrophils in appendicitis patients associated with EV is currently undefined. In a separate study, researchers compared 420 patients of AA in the non-EV group with 11 patients in the EV group and found no significant difference in neutrophil count and WBC.[17] However, the non-EV group displayed higher SII levels. The restricted number of EV patients (n=11) poses a significant limitation to this study. Additionally, the EV group exhibited a considerably lower inflammation rate (n=4, 57%) compared to our findings of a more closely aligned inflammation rate (46.8%). One study has concluded that EV does not cause appendicitis.[14] However, our elevated inflammation rate indicates that EV could potentially lead to appendicitis, although it may also be incidentally detected.

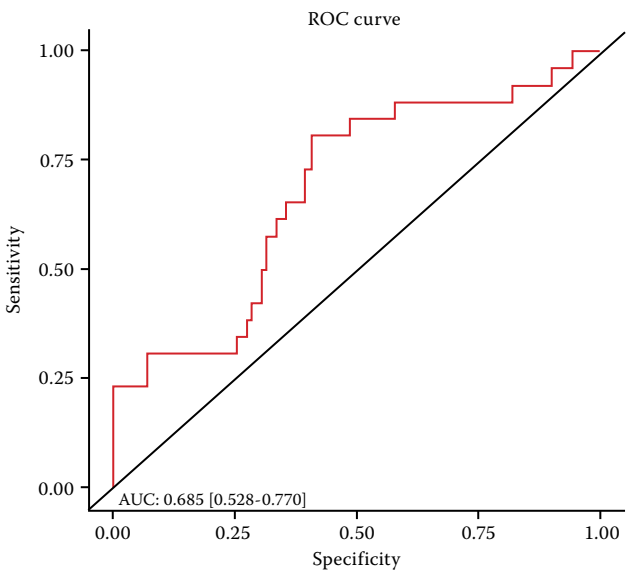

Figure 5. Receiver operating characteristic curve of the best model.

ROC: Receiver operating characteristic; AUC: Area under the curve.

Platelet distribution width is also a key parameter in the best model found in the present study. To our knowledge, PDW has not been studied in appendicitis associated with EV. We found no significant difference in univariable analysis, but PDW had a higher Z-score and lower p-value than another meaningful parameter neutrophil in the best model for predicting EV. The difference in PDW between surgically and medically treated adult AA patients has been studied, and lower PDW values were found in the surgically treated group.[18] This result seems to contradict our findings due to the lower inflammation in our EV group. However, most of the participants in our study were children (19 pediatric and seven adult patients in the EV group). Another study found no significant difference

in PDW between perforated and nonperforated appendicitis.[19] No significant differences between the groups in the present study; however, none of the studies developed a predictive model. Table 4 illustrates feasible reference cut-off values for detecting EV patients using PDW and neutrophil count. A neutrophil count of ≤8.91 displayed the greatest sensitivity (68.7%) with an acceptable specificity rate (50%) for a cut-off value. The low number of patients in the investigation could be the reason for this result. More comprehensive data is necessary to achieve better outcomes.

A significantly lower WBC was found in the EV group as compared to the non-EV group in this study, which is supported by several studies. Ozen et al.[20] found lower WBC, neutrophils, and CRP and higher eosinophils in patients with EV detected in the appendix vermiformis. Akkapulu and Abdullazade[21] also found lower WBC in the EV-detected group. Appendicitis with EV was shown to have less inflammation and lower SII.[17,20] Therefore, WBC may also be useful in the preoperative assessment of patients with acute abdomen. In our study, the median and 25th and 75th quartiles of WBC in the EV and non-EV groups were 12.8 (9.20-14.4) and 14.3 (10.9-16.9), respectively. If AA is suspected, a lower-than-usual leukocytosis may give an idea of EV. In such patients, it is important to inquire about symptoms and exposure history to EV infestation and consider performing a cellophane (scotch) tape test to aid in diagnosis and treatment. Antihelminthic therapy should be applied after an accurate diagnosis.

Accurately diagnosing EV infestation still presents significant challenges. While the gastrointestinal system is the primary site of infestation, infestation of the vulva and keratitis have been reported.[22-25] The main part of the parasite life cycle is in the gastrointestinal system. Therefore, the cellophane tape method is still the most sensitive laboratory test for diagnosis.[26] However, diagnosis depends on clinical symptoms in addition to the tape method. Most patients are asymptomatic, but perianal pruritus, insomnia, restlessness, and irritability may occur, particularly in children.[27] This asymptomatic clinical presentation in most patients makes diagnosis difficult. Therefore, new studies are needed to determine a biomarker for EV infestation. In our study, we investigated AA patients with EV detection. However, despite screening histopathology results of appendectomy material over the last 16 years, we found only 32 patients. Unfortunately, hemogram values were available in only 26 of these patients, which constituted a limitation of this study. Multicenter studies from different populations with more patients would give better results.

In conclusion, as one of the most common parasites in the world, EV can be a rare cause of appendicitis. It is difficult to predict the presence of the parasite before surgery when AA is suspected. However, WBC and neutrophil counts are lower than in the usual appendicitis, and a model composed of PDW and neutrophil count could give an idea about the parasite. The cellophane tape method could be used for early and fast diagnosis in suspected patients. Studies that collect large amounts of data from multiple centers and different populations could provide better predictive models. A model with a higher area under the curve closer to one could serve as a biomarker for EV in AA.

Ethics Committee Approval: The study protocol was approved by the Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee (date: 20.09.2023, no: 2023/0585). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from the parents and/or legal guardians of the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conceived and designed the study: A.S., H.S.; Collected, analyzed, and interpreted the data: A.S., H.S., A.I.A.; Drafted the manuscript: A.S. The authors contributed to the paper as follows.All authors reviewed and approved the final version.

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