Research Article (Araştırma Makalesi)

Predicting High Risk Patients for Negative Appendectomy and Severe Appendicitis Using Inflammatory Biomarkers

Enflamatuvar Biyobelirteçler Kullanılarak Negatif Apendektomi ve Şiddetli Apendisit İçin Riskli Hastaların Öngörülmesi

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Özet

Amaç: Bu çalışmanın amacı yetişkinlerde akut apandisit nedeniyle yapılan apendektomilerde negatif laparotomiyi ve akut apandisitin şiddetini ön görmede tam kan sayımının (CBC), enflamatuvar biyo-belirteçlerin, bu parametreler kullanılarak hesaplanan indekslerin ve C-reaktif protein (CRP) seviyelerinin etkinliğinin değerlendirilmesidir.

Gereç ve Yöntemler: Bu kesitsel ve gözlemsel çalışmaya Ocak 2015 ile Kasım 2020 tarihleri arasında apendektomi geçirmiş 1389 hasta dâhil edilmiştir. Hastaların yaşı, cinsiyeti ve preoperatif kan tahlillerindeki CRP değerleri, CBC'ye ait enflamatuvar parametreleri ve patolojik tanıları kaydedilmiştir. Gruplar arasında çok değişkenli analizler ve lojistik regresyon analizleri yapılmıştır.

Bulgular: Çok değişkenli analiz sonucunda beyaz küre sayısı (WBC), trombosit sayısı (PLT), ortalama trombosit volümü (MPV), mutlak nötrofil ve lenfosit sayıları, nötrofil oranı (%NEU), lenfosit oranı (%LYM), nötrofil/lenfosit oranı (NLR), platelet/lenfosit oranı (PLR) ve CRP/lenfosit oranı (CLR) negatif laparotomiyi anlamlı olarak predikte eden parametreler olarak belirlenmiştir (sırasıyla p<0.001; p=0.031; p=0.02; p<0.001; p<0.001; p<0.001; p<0.001; p<0.001; p=0.044 ve p=0.012). Aynı analizde yaş, CRP, plateletkrit, mutlak nötrofil sayısı, %NEU, NLR ve CLR ise akut apandisitin şiddetini anlamlı olarak öngören parametreler olarak belirlenmiştir (sırasıyla p=0.001; p<0.001; p=0.0,32; p=0.01; p=0.019; p=0.01 ve p<0.001). Bu parametrelerin lojistik regresyon denklemleri ile tekrar incelenmesi sonucunda NLR'nin negatif laparotomiyi öngörmedeki OR=1.737 (CI 1.275-2.366; p=0.001; 1-β err prob=0.993) ve CRP'nin komplike vakaları öngörmedeki OR= 1.783 (CI 1.529-2.08; p<0.001; 1-β err prob= 0.991) olarak hesaplanmıştır.

Sonuç: NLR, akut apandisiti olmayan vakaların tespitinde kolay ve pratikte uygulanabilir bir belirteçtir. CRP ise komplike akut apandisiti öngörmede en kıymetli biyobelirteçtir.

Anahtar kelimeler: Akut apandisit, Komplike apandisit, Nötrofil/lenfosit oranı, CRP, Negatif laparotomi

Abstract

Objective: The aim of the present study is to evaluate the value of inflammatory parameters and indices of complete blood count (CBC) and C-reactive protein (CRP) in predicting negative laparotomies and severity of acute appendicitis in adults.

Material and Methods: A total of 1389 patients who had undergone appendectomy between January 2015 and November 2020 were enrolled in this observational and cross-sectional study. Age, gender, preoperative CRP values, inflammatory parameters of CBC and the pathologic diagnosis were recorded. Multivariate analysis and logistic regression analysis were performed.

Results: In multivariate model white blood cell (WBC), platelet count (PLT), mean platelet volume (MPV), absolute neutrophil and lymphocyte counts, neutrophil percentage (NEU%), lymphocyte percentage (LYM%), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio and CRP-to-lymphocyte ratio (CLR) were significant discriminators of negative laparotomy (p<0.001; p=0.031; p=0.02; p<0.001; p<0.001; p<0.001; p<0.001; p<0.001; p=0.044 and p=0.012, respectively). Meanwhile age, CRP, plateletcrit, absolute neutrophil count, NEU%, NLR and CLR were significant predictors of severity (p=0.001; p<0.001; p=0.032; p=0.01; p=0.019; p=0.01 and p<0.001, respectively). These parameters were reanalyzed in the logistic regression equations. The OR of NLR was 1.737 (CI 1.275-2.366; p=0.001; 1-β err prob=0.993) for predicting negative laparotomy and the OR of CRP was 1.783 (CI 1.529-2.08; p<0.001; 1-β err prob=0.991) for predicting complicated cases.

Conclusion: Neutrophil-to-lymphocyte ratio is an easy and feasible marker to exclude patients without appendicitis whereas CRP is the most valuable predictive biomarker of complicated appendicitis.

Keywords: Acute appendicitis, Complicated appendicitis, CRP, Negative laparotomy, Neutrophil-to-lymphocyte ratio

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INTRODUCTION

Acute abdominal pain constitutes approximately 7-10% of admissions in emergency service (1) and approximately 2% of these patients diagnosed as acute appendicitis (AA) (2). Although simple appendicitis has a mortality rate less than 0.1%, it has recently been reported that the mortality rate of complicated AA increased (gangrenous appendicitis is 0.6% and of perforated appendicitis is nearly 5%) (1). Additionally, infrequent complications related to perforation of acute appendicitis carry even higher mortality rates (3). On the other aspect of the issue, the negative laparotomy rate is 15-30% worldwide (4). Negative laparotomy rate is certainly lower in settings that liberally use imaging modalities like Ultrasound (USG) and Computerized Tomography (CT), but it is a fact that in lower in-come settings and in rural areas authorities might not be able to provide the necessary equipment and trained personnel for these modalities.

In recent years several well designed and qualified researches demonstrated that if acute appendicitis is recognized in the early phase, conservative antibiotics therapy yields similar results as surgical approach (5). This change in the paradigm certainly is a milestone and palliates the surgical burden in many aspects. Timely and correct diagnosis of acute appendicitis and valid identification of the complicated cases would ensure the opportunity of conservative therapy for patients with simple appendicitis. Additionally, it would prevent unnecessary radiation exposure, negative laparotomies and accordingly reduce morbidity and mortality rates as well as hospital costs (6). Therefore, both enhancing the accuracy in diagnosis and discriminating between the simple and complicated cases are essential.

Although the diagnosis is classically based on clinical findings, several biomarkers were studied for the aid of diagnosis as well as for the discrimination between simple and complicated cases (6,7). But the results are contradictory and high quality information is missing (5). In 2020 update of the World Society of Emergency Surgery (WSES) Jerusalem Guidelines, it is stated in Statement 1.6 as follows; "Biochemical markers represent a promising reliable diagnostic tool for the identification of both negative cases and complicated acute appendicitis in adults. However, further high-quality evidence is needed" (1). The quality of evidence is low and there is no recommendation regarding the statement (1). It is important to emphasize that these parameters are a part of routine preoperative evaluation worldwide. They are easily performed, quickly responsive and cost effective in nearly all emergency settings (8). Consequently, if actually precise guidance along the diagnosis and management of acute appendicitis would be provided by these markers, high quality evidence-based information should be pursued.

The aim of the present study is to evaluate the value of inflammatory parameters and indices of complete blood count (CBC) and C reactive protein (CRP) in discriminating negative laparotomies as well as predicting the complicated acute appendicitis in adults.

MATERIALS AND METHODS

This observational and cross-sectional study was methodologically designed and conducted according to the checklist of items of STROBE Statement (9). All the procedures in this study were in compliance with the institutional and national research committee ethical standards and the 1964 Helsinki Declaration and its later amendments. Approval for the study was granted by Omer Halisdemir University Ethics Committee (12.11.2020; 2020/63).

The electronic medical records of Omer Halisdemir University Training and Research Hospital were evaluated and anonymous historical records of 1927 adult patients who had undergone appendectomy between January 2015 and November 2020 were detected. Patients younger than 18 years old, pregnant women, patients who had incidentally appendectomy in operations for other reasons (colon malignancies, ischemic necrosis, generalized brid ileus etc.) and patients with pathologic reports of primary or metastatic appendix malignancies were excluded.

For each patient included into the analysis, the last studied laboratory tests before the appendectomy operation were obtained. Age, gender, CRP values and inflammatory parameters of CBC, namely white blood cell (WBC), platelets (PLT), red cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV), plateletcrit (PCT), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), neutrophil percentage (NEU%), lymphocyte percentage (LYM%) as well as the pathologic diagnosis were recorded for each patient. The indices, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and CRP-to-lymphocyte ratio (CLR) were also calculated and recorded. NLR was calculated by the formula

(ANC/ALC) and PLR was calculated by the formula (PLT/ALC). CLR was calculated by the formula (CRP/ALC) x100.

Statistical Analysis and Power Analysis

IBM Statistical Analysis for Social Sciences (SPSS) version 22 (IBM, Chicago) was used for statistical analysis. The descriptive statistics were expressed as mean SD for continuous variables and as % (range) for categorical variables. The descriptive characteristics were compared with either Student's t test or Mann-Whitney U test where appropriate due to the distribution of the variable. The categorical variables were compared with Pearson χ^2 test. MANOVA test was performed in order to determine the parameters that are fit for logistic regression analysis. Logistic regression analysis was undertaken to determine the independent parameters and were expressed by OR. Any P values <0.05 was accepted as statistically significant. Effect size calculations were performed by using either Psychometric Freeware of Computation of Effect Sizes (https://www.psychometrica.de/effect_size.html) or IBM SPSS Statistics 22 version.

For power analysis calculations G*Power 3.1 (10,11) was used. For overall power of the study a posthoc power analysis was conducted using to test the difference between two independent group means using a two-tailed test, a strong effect size (d=0.99), and an alpha of 0.05. Result showed that both a total sample of 1389 participants (1213 acute appendicitis and 176 negative laparotomy) for diagnosis and a total sample of 1213 participants (1095 simple appendicitis and 118 complicated appendicitis) for severity achieve a power of 1.0. Using the same software, the power of the given OR with given sample sizes with an alpha of 0.05 using binominal distribution were calculated for all constructed logistic regression models and were shown in tables with the relevant OR values.

RESULTS

There were 1927 adult appendectomy cases and after applying the exclusion criteria there were 1872 patients left. Among these, 483 patients had either absent CRP or some CBC parameters in their records and were excluded from the study. Finally, there were 1389 adult appendectomy records appropriate for statistical analysis.

The rate of negative laparotomy was 12.7% and of complicated appendicitis was 9.7% (**Table 1**). Women had significantly higher negative laparotomy rates when compared with men (p=0.003).

The descriptive features and univariate statistics between negative laparotomy and acute appendicitis are summarized in **Table 2**. WBC, ANC, NEU% and LYM% were significantly different between negative laparotomy and acute appendicitis with medium effect sizes (**Table 2**). The descriptive features and univariate analysis between simple appendicitis and complicated appendicitis are shown in **Table 3**. CRP and CLR were significantly higher in complicated appendicitis with medium effect sizes (**Table 3**).

In posthoc analysis of multivariate linear model, WBC, PLT, MPV, ANC, ALC, NEU%, LYM%, NLR, PLR and CLR were independent parameters of negative laparotomy (**Table 4A**). The predictors of complicated appendicitis were age, CRP, PCT, ALC, NEU%, NLR and CLR (**Table 4B**). The flow chart demonstrating the study groups and the results of univariate and multivariate analyses between groups is shown in **Figure 1**.

After specifying the variables fit for model, the binary logistic regression equations were constructed. ANC, ALC, NEU% and LYM% were represented by NLR in the first model; PLT, ALC, NEU% and LYM% were represented by PLR in the second model and finally ALC, NEU% and LYM% were represented by CLR in the third model. The reason was to prevent the situation

Table 1. Gender distribution and frequency of negative laparotomy, simple and complicated appendicitis in the study population

	Total	Women	Men	p	Cramer's V
Negative laparotomy	176 (12.7)	93 (15.8)	83 (10.4)	0.003	0.08
Acute appendicitis	1213 (87.3)	496 (84.2)	717 (89.6)		
Simple acute appendicitis	1095 (90.3)	447 (90.1)	648 (90.4)	0.883	
Complicated acute appendicitis	118 (9.7)	49 (9.9)	69 (9.6)		

Table 2. Descriptive characteristics of patients with acute appendicitis and negative laparotomy					
	Total Mean±SD	**Negative laparotomy Mean±SD**	**Acute appendicitis Mean±SD**	***p***	**Effect size**
Age	35.7±15.7	37.3±16.1	35.7±15.7	0.143	
CRP	42.7±65.8	35.2±53	43.8±67.4	0.025	0.004 [1]
WBC	13.8±4.6	11.36±4.05	14.17±4.56	0.0001	0.625 [2]
PLT	251.3±64.9	261.92±74.46	249.77±63.12	0.02	0.188 [2]
RDW	13.4±1.6	13.74±2.5	13.4±1.48	0.079	
PDW	15.6±1.8	15.88±1.62	15.63±1.81	0.061	
MPV	9.3±1.3	9±1.45	9.3±1.32	0.004	0.224 [2]
PCT	0.34±0.5	0.29±0.39	0.34±0.5	0.212	
ANC	10.8±4.7	8.17±3.99	11.2±4.43	0.0001	0.692 [2]
ALC	2.1±2.4	2.27±0.97	1.98±0.86	0.0001	0.332 [2]
NEU%	76.1±11.1	69.17±12.23	77.31±9.96	0.0001	0.792 [2]
LYM%	16.4±9.2	22.36±10.64	15.53±8.48	0.0001	0.778 [2]
NLR	7.07±7.01	5.49±11.69	7.3±6.01	0.0001	0.051 [1]
PLR	152.25±113.5	147.91±187.86	154.02±98.33	0.008	0.006 [1]
CLR	3.12±6.61	2.43±4.65	3.22±6.85	0.002	0.007 [1]

[1] n2 for Mann Whitney U test
[2] Cohens's d for Student t Test
CRP: C-Reactive protein, WBC: White blood cell, PLT: Platelet, RDW: red cell distribution width, platelet distribution width, MPV: mean platelet volume, PCT: Plateletcrit, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, NEU%: Neutrophil percentage, LYM% Lymphocyte, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CLR: CRP-to- lymphocyte ratio

Table 3. Descriptive characteristics of patients according to severity				
	Simple appendicitis Mean±SD	**Complicated appendicitis Mean±SD**	***p***	**Effect Size**
Age	34.9±15.3	39.9±17.7	0.003	0.324 [1]
CRP	38±61.2	96.5±94.5	0.0001	0.062 [2]
WBC	14.18±4.58	14.04±4.37	0.76	
PLT	250.18±62.33	245.94±70.21	0.489	
RDW	13.37±1.47	13.6±1.56	0.125	
PDW	15.62±1.8	15.71±1.87	0.601	
MPV	9.29±1.31	9.48±1.3	0.13	
PCT	0.35±0.51	0.24±0.16	0.0001	0.226 [1]
ANC	11.18±4.44	11.33±4.26	0.728	
ALC	2.01±0.86	1.73±0.72	0.0001	0.33 [1]
NEU%	77.1±10.12	78.33±8.04	0.007	0.124 [1]
LYM%	15.74±8.61	13.54±6.87	0.002	0.26 [1]
NLR	7.15±5.6	8.5±8.81	0.024	0.006 [2]
PLR	151.76±98.06	169.4±103.83	0.013	0.006 [2]
CLR	27.89±64.62	71.45±88.45	0.0001	0.068 [2]

[1] Cohens's d for Student t Test
[2] n2 for Mann Whitney U test
CRP: C-Reactive protein, WBC: White blood cell, PLT: Platelet, RDW: red cell distribution width, platelet distribution width, MPV: mean platelet volume, PCT: Plateletcrit, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, NEU%: Neutrophil percentage, LYM% Lymphocyte, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CLR: CRP-to- lymphocyte ratio

Table 4. Multivariate analysis of variables. PostHoc analysis for negative laparotomy and severity

	Post Hoc for negative laparotomy				Post Hoc for severity			
	p	**%95 CI (Lower Upper)**		**R^2**	***p***	**%95 CI (Lower Upper)**		**R^2**
Age					0.001	-8.28	-2.26	0.009
CRP					0.0001	-1.69	-1.08	0.061
WBC	0.0001	2.18	3.64	0.043				
PLT	0.031	-22.25	-1.08	0.003				
RDW								
PDW								
MPV	0.02	0.04	0.47	0.005				
PCT					0.032	0.008	0.19	0.003
ANC	0.0001	2.4	3.82	0.052				
ALC	0.0001	-0.41	-0.12	0.019	0.01	0.11	0.46	0.019
NEU%	0.0001	6.49	9.84	0.071	0.019	-4.39	-0.39	0.071
LYM%	0.0001	-8.31	-5.4	0.07				
NLR	0.0001	0.36	0.59	0.054	0.01	-0.32	-0.04	0.054
PLR	0.044	0.02	0.16	0.007				
CLR	0.012	0.07	0.63	0.065	0.0001	-1.87	-1.2	0.065

CRP: C-Reactive protein, WBC: White blood cell, PLT: Platelet, RDW: red cell distribution width, platelet distribution width, MPV: mean platelet volume, PCT: Plateletcrit, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, NEU%: Neutrophil percentage, LYM% Lymphocyte, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CLR: CRP-to- lymphocyte ratio

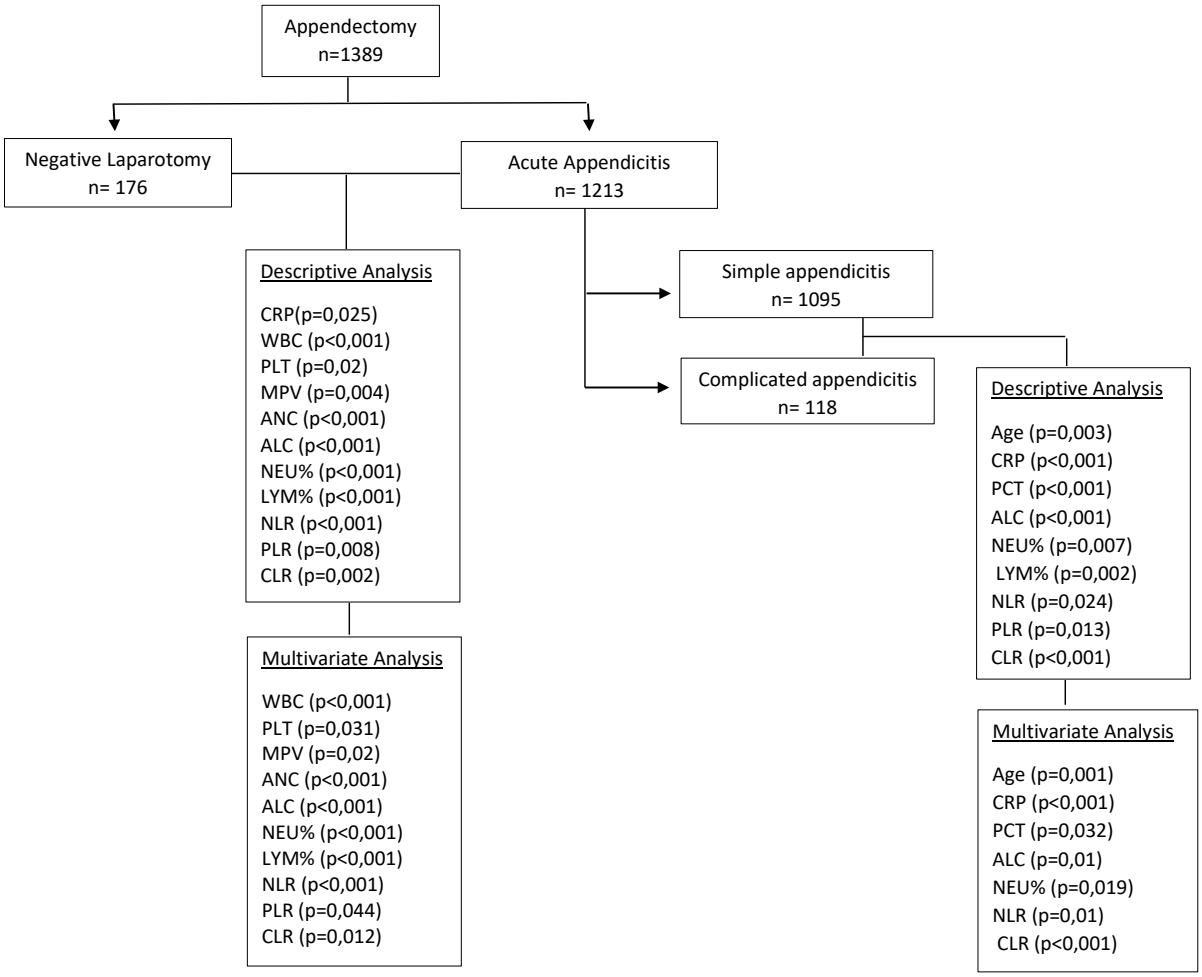

Figure 1. Flow chart demonstrating the study groups and the results of univariate and multivariate analyses between study groups.

known as Simpson's paradox, described as competing of similar parameters for being the best choice (12). For the same reason CRP and CLR were used separately to construct two individual models that predict severity in order to prevent the interference of CRP and CLR with each other.

All the parameters of the first logistic regression model were statistically significant in discriminating patients with negative laparotomy (**Table 5A**). The odds ratios were 1.118 (CI 1.061-1.179; p<0.001) for WBC, 0.997 (CI 0.994-0.999; p=0.014) for PLT, 1.165 (CI 1.021-1.329; p=0.023) for MPV and 1.737 (CI 1.275-2.366; p=0.001) for NLR. NLR had the most predictive OR. In the second equation all parameters other than PLR were significant parameters of negative laparotomy (**Table 5B**). The odds ratios were 0.707 (CI 0.566-0.884; p=0.002) for WBC, 1.170 (CI 1.027-1.332; p=0.018) for MPV, 1.724 (CI 1.357-2.19; p<0.001) for ANC and 0.608 (CI 0.362-1.022; p=0.06) for PLR. ANC had the most predictive OR in this equation. The third equation revealed that PLT, MPV and ANC were independent variables of negative laparotomy (p=0.017, p=0.022 and p=0.003 respectively) (**Table 5C**). The relevant ORs were as follows; 0.997 (CI 0.994-1.999), 1.166 (CI 1.022-1.331) and 1.31 (CI 1.094-1.568) arranged in order. The 1-β error probabilities for the ORs of significant variables were 0.05, 0.215 and 0.55 respectively, demonstrating that none of the parameters of this equation had predictive ORs for discriminating negative laparotomy.

In the fourth model only CRP (OR=1.783; CI 1.529-2.08; p<0.001) and in the fifth model only CLR (OR=1.77; CI 1.522-2.059; p<0.001) were significant parameters of the regression equations (**Table 6A** and **6B**). The predictivities of ORs of CRP and CLR were of very high strength (0.991 and 0.989 respectively).

DISCUSSION

The main outcome of the present study is that out of CRP and the inflammatory biomarkers and indices of CBC, neutrophil-to-lymphocyte ratio is the most powerful independent marker of negative laparotomy whereas CRP is the unique and a powerful predictor of complicated appendicitis.

The symptomatology of many several gynecologic diseases, like ovarian torsion, pelvic inflammatory disease and ectopic pregnancy or even physiologic conditions related to ovulation and menstruation may easily overlap with acute appendicitis in women at premenopausal period (13). Accordingly, in the present study the negative laparotomy rates were significantly higher in women than in men, whereas the rates of complicated appendicitis were similar in both gender.

The indices calculated by dividing either neutrophil count, platelet count or CRP level by lymphocyte count (NLR, PLR and CLR respectively) were regarded as promising biomarkers for distinguishing inflammatory processes (14,15). NLR is the most extensively studied

Table 6. Binary logistic regression analysis equations for CRP and CRP to lymphocyte ratio

	CRP						CLR				
	B	*p*	OR	%95 CI (Lower Upper)		1-β err (Power)	B	*p*	OR	%95 CI (Lower Upper)		1-β err (Power)
Age	0.005	0.449	1.005	0.993	1.017		0.004	0.464	1.004	0.993	1.017	
CRP	0.578	0.0001	1.783	1.529	2.08	0.991						
PCT	-0.79	0.105	0.455	0.176	1.178		-0.65	0.137	0.52	0.22	1.231	
NLR	0.26	0.254	1.296	0.83	2.025		0.14	0.533	1.151	0.74	1.788	
PLR	-0.13	0.659	0.876	0.488	1.575		-0.47	0.12	0.625	0.345	1.131	
CLR							0.571	0.0001	1.77	1.522	2.059	0.989

CRP: C-Reactive protein, WBC: White blood cell, PLT: Platelet, RDW: red cell distribution width, platelet distribution width, MPV: mean platelet volume, PCT: Plateletcrit, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, NEU%: Neutrophil percentage, LYM% Lymphocyte, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CLR: CRP-to- lymphocyte ratio

Table 5. Binary logistic regression analysis. Equations for A. Neutrophil to lymphocyte ratio B. Platelet to lymphocyte ratio C. CRP to lymphocyte ratio

	A.Neutrophil to lymphocyte ratio							**B. Platelet to lymphocyte ratio**							**C. CRP to lymphocyte ratio**					
	B	***P***	**OR**	**%95 CI (Lower-Upper)**		**1-β err (Power)**		**B**	***P***	**OR**	**%95 CI (Lower-Upper)**		**1-β err (Power)**		**B**	***P***	**OR**	**%95 CI (Lower-Upper)**		**1-β err (Power)**
WBC	0.112	0.0001	1.118	1.061	1.179	0.134	WBC	-0.347	0.002	0.707	0.566	0.884	0.683	WBC	-0.083	0.349	0.921	0.774	1.095	
PLT	-0.003	0.014	0.997	0.994	0.999	0.05	PLT							PLT	-0.003	0.017	0.997	0.994	0.999	0.05
MPV	0.153	0.023	1.165	1.021	1.329	0.213	MPV	0.157	0.018	1.17	1.027	1.332	0.223	MPV	0.154	0.022	1.166	1.022	1.331	0.215
ANC							ANC	0.544	0.0001	1.724	1.357	2.19	0.991	ANC	0.27	0.003	1.31	1.094	1.568	0.55
NLR	0.552	0.0001	1.737	1.275	2.366	0.993	NLR							NLR						
PLR							PLR	-0.498	0.06	0.608	0.362	1.022		PLR						
CLR							CLR							CLR	0.084	0.107	1.088	0.982	1.205	

CRP: C-Reactive protein, WBC: White blood cell, PLT: Platelet, RDW: red cell distribution width, platelet distribution width, MPV: mean platelet volume, PCT: Plateletcrit, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, NEU%: Neutrophil percentage, LYM% Lymphocyte, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CLR: CRP-to- lymphocyte ratio

inflammatory index following the first introduction in 1995 (16). WBC and ANC are early reagents in human body against acute inflammation (17). Therefore, the sensitivity for acute appendicitis and predictivity of negative laparotomy is quite variable (17). NLR, on the other hand, combines the two pathways of inflammation and increases the sensitivity for detection of various inflammatory processes (18). The clinical efficacy of NLR in diagnosis of acute appendicitis has been validated by various studies (18). In a recently published article NLR had %86.1 sensitivity for appendix diameter equal to or greater than 6mm (19). Similarly, a retrospective analysis revealed a sensitivity value of 75% and a specificity of 68% for diagnosing acute appendicitis (20). Prospectively in a clinical trial NLR was found to be higher in complicated cases than uncomplicated appendicitis (21). Consequently, NLR levels were significantly higher in acute appendicitis patients than patients with negative laparotomy and in complicated appendicitis than in simple appendicitis in a recent meta-analysis pooling the data of 17 studies (18). It is of note that CRP was not one of the outcomes in the mentioned study and hence was not compared with NLR in severity prediction. The results of the present study confirm that NLR is significantly lower in negative laparotomies, NLR is an independent predictor of negative laparotomy and is the only index that had the OR with sufficient predictivity.

Platelet activation and turnover was shown to be increased as a response to inflammatory processes (17). In high-inflammatory acute conditions the mechanism involves the enlargement and activation of platelets (22) as well as the sequestration and destruction of large and active platelets (17). Therefore, the mechanism of platelet and related indices' response to inflammation is complex, multidimensional and might be unpredictable in some situations. MPV, PDW and PLR were the most widely studied platelet indices of inflammation yet with controversial results (17,23). In a prospective study PDW was found to be useful in diagnosis of acute appendicitis when used in combination with elevated WBC and neutrophil counts (17). In the same study MPV and RDW levels were proven to be useless as diagnostic parameters in acute appendicitis (17). On the other hand, a meta-analysis on diagnostic value of MPV on acute appendicitis concluded that MPV values might be a potential marker for diagnosis of acute appendicitis (24). The results of the present study showed that RDW and PDW levels were statistically insignificant between acute appendicitis and negative laparotomy cases. Otherwise in univariate analysis MPV was significantly higher in acute appendicitis, was an independent discriminator of negative laparotomy in the final regression models, but the strength of evidence level was low as OR demonstrated a predictivity of only 0.2. The situation is not very different with PLR. Previous reports revealed that the PLR levels were significantly higher in acute appendicitis and complicated appendicitis when compared to negative laparotomy cases (25). In a meta-analysis, the authors pooled the data of 11 studies (26). The PLR levels were significantly higher in acute appendicitis patients (26). However, it was not significantly different between simple and complicated cases (26). Similarly, in the present study mean values were higher in acute appendicitis than negative laparotomy and was higher in complicated cases. But in the final regression model PLR was not an independent predictor for acute appendicitis.

Readily perforation of appendix and higher rates of complicated cases are encountered in both ends of the age spectrum (5). This old standing information was verified by the results of the present study once again. Although individuals younger than 18 years old were not the subject of research, this study confirmed with a medium effect size that patients with complicated appendicitis tend to be older than counterparts with simple appendicitis. Besides age remained to be a significant part of the severity prediction in multivariate analysis, but finally logged out from the logistic regression model leaving CRP solely as a predictor of complicated disease. CRP is an acute phase reactant and one of the most studied biomarkers for all inflammatory processes (27). Differential diagnosis of acute appendicitis includes acute ileitis, Crohn's disease, gynecologic and obstetrical conditions, urologic conditions (28) and therefore this population already have some inflammatory processes going on. On the other hand, as acute appendicitis gets complicated, the inflammatory burden increases dramatically and CRP gets involved in differentiation as a marker (14). Recently the likelihood of complicated appendicitis, presented as higher rates of conversion from laparoscopic approach to open, was found to be associated with higher preoperative CRP levels (29). Meanwhile increasing CRP, as well as WBC, was found to be correlated with an increased likelihood of complicated appendicitis (30). In a case controlled retrospective study CRP was the only significant factor in the logistic regression equation modelled for predicting complica-

ted acute appendicitis (5). Also previously CRP was reported to be more sensitive for perforated cases than for discriminating between patients with and without AA (31).

The outcome of the present study validates the mentioned previous findings. Additionally, interpretation of the results of this study would end up with more effective integration of CRP into clinical practice for severity prediction. CLR, an easily calculated biomarker was found to be significant in discriminating perforated cases (32). However, CRP has OR with similar power and CLR has no advantage over CRP nevertheless.

The discrepancy on this issue between published data mainly depends on the fact that in most of the studies univariate analysis were performed and several contributing factors were neglected (5). Other reasons include inappropriate statistical analysis, inadequate sample size and consequently insufficient power attributed to the study. One of the main advantages of this study is that the sample size is very large. Additionally, the statistical methods are based on multivariate analysis and results are interpreted in combination of statistical significance and effect sizes.

The main limitations of the present study are the retrospective design and the study population. In order to minimize the bias attributed to retrospective data collection, first of all, the records with any missing data were excluded from the analysis. Additionally, quantitative data measured and kept by automated systems was the subject of this study, not subjective information which can be misleading. The most important factor limiting the study was the patient population which constituted of patients who already had the diagnosis of acute appendicitis. In fact, the ideal population for studying diagnostic predictivity would be the patients with suspected acute appendicitis, not somehow diagnosed.

Conclusion

Definitely there are many inflammatory markers and many models constructed by using inflammatory markers for predicting diagnosis and severity of acute appendicitis. But feasibility, cost effectiveness and prompt responsiveness are all essential features. When these features are combined and melted in the same pot for a biomarker, simple biochemistry and simple CBC is what we can do most of the time and in most of the emergency settings all around the world. Our results demonstrated that neutrophil-to-lymphocyte ratio is the most powerful index out of the CBC parameters in foreseeing the probability of negative laparotomy in acute appendicitis whereas CRP remains the most valuable predictive biomarker of complicated appendicitis in adult emergency settings. Finally, we can conclude that if prospective validation of these results can be achieved, NLR, as a predictor of negative cases and CRP, as a predictor of complicated ones, can be incorporated into the eligible guidelines in the future.

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Author Contribution: All authors contributed equally to the article.

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