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ORIGINAL ARTICLE

Prospective validation of neutrophil-to-lymphocyte ratio as a diagnostic and management adjunct in acute appendicitis

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Abstract
Background No optimal biomarker exists that accurately diagnoses appendicitis or predicts severity, estimates post-operative complications or total length of hospital stay (LOS).
Aim To prospectively validate the utility of neutrophil-to-lymphocyte (NLR) ratio in predicting the severity of appendicitis, LOS, and 30-day complication rates.
Methods Patients who were admitted with a provisional diagnosis of acute appendicitis over a period of 18 months (Oct 2014–April 2016) were included. Patient demographics and blood results were prospectively collected. Details of imaging, operative intervention, severity of appendicitis, length of stay, and 30-days post admission complications were recorded. Recommended cut-off values of NLR and C-reactive protein for severity of appendicitis were determined using receiver operating characteristic analysis (ROC). These cut-off values were compared with C-reactive protein levels. Mann-Whitney test was performed to assess the correlations between LOS and 30-day complications to NLR.
Results Four hundred fifty-three patients were included in the study; 55.2% ($n = 245$) were female with mean patient age of 23 years. Two-thirds ($n = 281$, 62.03%) underwent operative management. Histologically, appendicitis was confirmed in 214 (76%) patients. A NLR of >6.36 or CRP of >28 were statistically associated with complicated acute appendicitis, with a median of one extra hospital day ($p < 0.0001$). Mean NLR was statistically higher in patients with post-operative complications (14.42 vs. 7.29 for simple appendicitis group, $p < 0.001$).
Conclusion This confirms previous reports that NLR is a simple, readily available adjunct in predicting severity of appendicitis. Additionally, it can aid delineating severe appendicitis that should proceed to surgery without substantial delay.

Keywords Appendicitis · Neutrophil-to-lymphocyte ratio · Post-operative outcomes

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Introduction

Acute appendicitis is a common surgical admission which requires early diagnosis and prompt management. Lifetime risk is approximately 10% [1]. One-fifth of the patients have severe appendicitis. Expeditious treatment is 'key', as this cohort of patients have associated higher morbidity [2, 3].

Traditionally, the diagnosis of appendicitis is based on clinical judgement. However, numerous publications report a range of adjuncts to help formulate decision-making in difficult scenarios [4]. Some surgeons utilize scoring systems like Alvarado and RIPASA to aid in the diagnosis [5, 6]. Modelled decision support systems are being developed [7]. Additionally, the role of routine radiological assessment is contentious, and there is debate regarding which modality to use [8].

A Cochrane review in 2011 highlighted that in selected patients, some could be managed conservatively with antibiotics [9]. Recent randomized controlled trials including meta-analyses have supported this management approach [10–13].

Table 1 Patient demographics, laboratory results, and LOS for each group (G1—complicated/severe appendectomy, G2—uncomplicated/simple appendicitis, G3—negative appendicitis)

	Total number	Gender	Mean age–years (range)	Mean CRP	Mean NLR	Mean LOS-days (range)
Cohort 1	41	Male: 23 Female: 18	26 (6–86)	81	11.4	4 (2–17)
Cohort 2	188	Male: 98 Female: 90	21.9 (3–60)	49	8.8	3.1 (1–7)
Cohort 3	36	Male: 16 Female: 20	14.9 (7–37)	16.4	4.7	3 (1–9)

G1 severe appendicitis, *G2* simple appendicitis, *G3* negative appendectomy

However, for this strategy to be successful, it is vital that patients with simple uncomplicated appendicitis are delineated and commenced on early antibiotic therapy [13, 14]. We have already shown neutrophil-to-lymphocyte (NLR) ratio as a useful adjunct in predicting the severity of appendicitis, post-operative complications, and length of stay [15].

NLR is a useful, simple, and inexpensive marker of subclinical inflammation, which is easily calculated from the differential white cell count (WCC) [16]. It has been shown that it provides information regarding two different immune and inflammatory pathways (acute inflammation and regulatory pathway) [17].

Already, NLR has been demonstrated to correlate with acute activity in other inflammatory conditions like inflammatory bowel disease and acute cholecystitis [18, 19]. There has been growing interest in evaluating the correlation of NLR with the outcome of different cancers like colorectal, gastric, and other solid neoplasms [20–22].

The role of NLR in appendicitis has been examined by other investigators after our retrospective series [8, 23–27]. One of the publications examined the correlation of NLR in diagnosing appendicitis in pregnancy [27]. Another group of authors reported that their analysis using the correlation of NLR to length of stay was equivocal [24].

However, the majority of data to date on NLR predictive value is retrospective. Our aim was to prospectively examine the role of NLR in assessing the severity of appendicitis, length of stay, and rate of post-operative complications.

Methods

Prospective data was recorded over a period of 18 months (October 2014–April 2016). Details of all patients admitted with the presumptive diagnosis of acute appendicitis were recorded, including patient demographics, laboratory tests (WCC, C-reactive protein), and use of any radiological imaging (ultrasound or computed tomography). Severe (complicated) appendicitis was defined as the presence of phlegmon or appendiceal mass on imaging. NLR was calculated using the differential white cell count. Treatment decision of operative or conservative management was recorded. Patients that had evidence of appendicitis on radiological

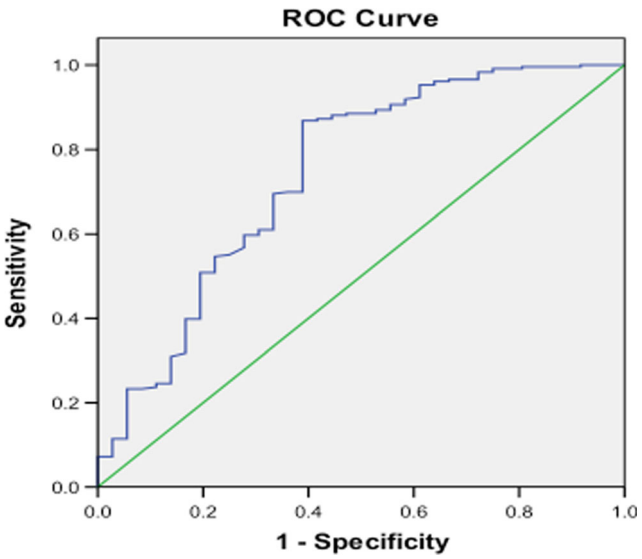

Fig. 1 ROC analysis curve for negative versus positive appendicitis using NLR

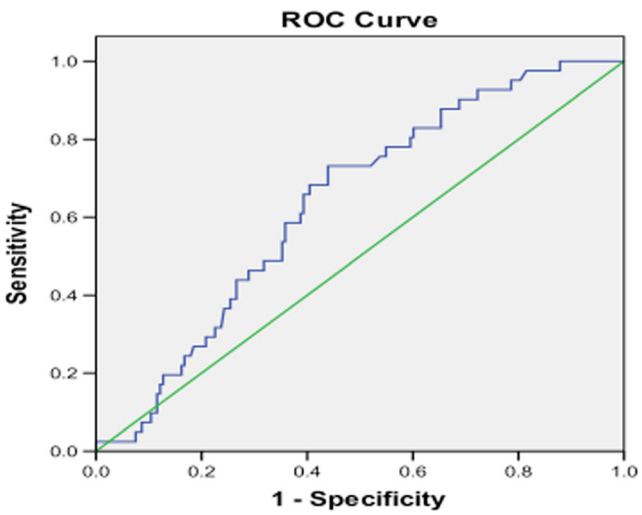

Fig. 2 ROC analysis curve for uncomplicated/simple versus complicated/severe appendicitis using NLR

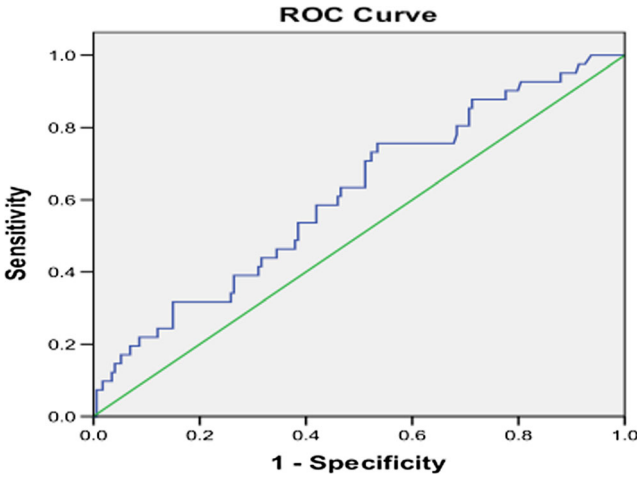

Fig. 3 ROC analysis curve for uncomplicated/simple versus complicated/severe appendicitis using CRP

imaging, but managed conservatively, were also included in the study. Post-operative length of stay (LOS) and histological severity of inflammation of appendix was also noted.

We also recorded any readmission to hospital including the reason for re-attending and any post-operative complications after discharge (identified either in surgical outpatient clinics or via general practitioner correspondence).

The entire cohort of patients was divided into three separate groups. One group (cohort 1) included patients with complicated/severe appendicitis (phlegmonous or gangrenous) with evidence either on histology or radiological imaging suggestive of appendicular mass; the second (cohort 2) comprised uncomplicated/simple acute appendicitis as indicated by histology; and the final group (cohort 3) had a normal appendix on histology.

Statistical analysis was performed using SPSS 20. Data was shown as mean ± standard deviation or median (range) where applicable. Recommended cut-off values of NLR for positive and negative appendectomies were determined using receiver operating characteristic (ROC) analysis.

This analysis was also performed for severity of appendicitis. With each cut-off value, sensitivity and specificity for each group were plotted, generating an ROC curve. ROC analysis was also used to determine whether CRP was also predictive of severity of appendicitis, and a cut-off value was established. A p value < 0.05 was considered statistically significant.

Mann-Whitney test was performed to assess if there was a difference in LOS between uncomplicated/simple and complicated/severe appendicitis. Additionally, Mann-Whitney test was utilized to assess if NLR cut-off value for predicting severity was useful in anticipating LOS. Finally, causes for 30-day post-operative readmission were evaluated, and the correlation to NLR value was assessed using student's t test.

Results

Over the 18 months study period (Oct 2014 to April 2016), 453 patients with a presumed diagnosis of acute appendicitis were admitted. Female gender was more common (n = 245, 55.2%). Median age across the cohort was 18 years (range 3–86). Average (median/range) LOS for the entire cohort was 3.1 days (3 days, 1–17).

Two hundred eighty-one patients (62%) were managed operatively. In the non-operative cohort (n = 172, 37.9%), 101 (58.3%) had normal imaging and were discharged

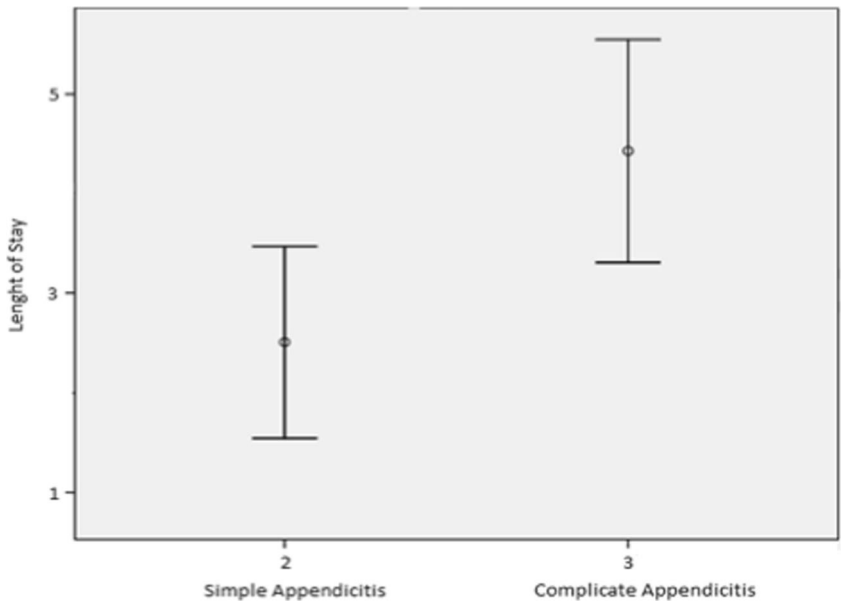

Fig. 4 Difference in median length of stay between uncomplicated/simple and complicated/severe appendicitis (p < 0.0001 Mann-Whitney test)

Table 2 Major post-operative 30-day complications for each group

Uncomplicated/simple appendicitis	Number
Wound dehiscence	1
Post-operative abdominal pain issues—adhesion related	3
Intra-abdominal collection	2
Wound infection requiring intravenous antibiotics	3
Complicated/severe appendicitis	
Post-operative abdominal pain issues—adhesion related	1
Wound infection requiring intravenous antibiotics	3
Intra-abdominal collection	2

when clinically improved. Twenty-five patients managed non-operatively had no imaging performed. They were managed with intravenous (IV) antibiotics (amoxicillin/clavulanic acid or cefuroxime + metronidazole) and were discharged on oral equivalents when clinical improvement was noted. Twenty-four patients had an alternative surgical or gynaecological diagnosis and managed accordingly. Twenty-two patients had an inflammatory appendiceal mass or phlegmon on radiological imaging and managed conservatively with IV antibiotics. One patient admitted with presumptive appendicitis was noted to have a caecal tumour on computed tomography scan. The patient had oncological staging and proceeded to have right hemicolectomy at a later date.

Eighty-nine percent of the appendectomies were performed laparoscopically. Out of the 281 appendectomies, 13 had evidence of parasitic infestation on histological examination and 3 had neuroendocrine tumours (of appendix). These patients were excluded from data analysis. Forty-one patients (14.6%) had complicated/severe appendicitis (cohort 1—including those with evidence on histology along with patients who were managed conservatively and had evidence of appendicular inflammatory mass on imaging), 188 patients (66.9%) had evidence of uncomplicated/simple appendicitis on histology (cohort 2), and 36 patients (12.8%) had a normal appendix histologically (cohort 3).

Mean NLR for negative appendectomy was 4.7 compared with 8.8 and 11.4 for uncomplicated/simple and complicated/severe appendicitis, respectively. Mean CRP was 16.4 for negative appendectomy compared with 49 and 81 for simple appendicitis and severe appendicitis, respectively (Table 1 outlines patient demographics, laboratory results, and LOS for each group). The recommended cut-off value of the NLR for positive appendectomy based on ROC analysis was 5.55 (sensitivity 0.61, specificity 0.70). Area under ROC curve was 0.74 (95% confidence interval [CI] 0.64–0.84 $p < 0.0001$) (Fig. 1). The cut-off value for NLR that predicted complicated/severe appendicitis was 6.36 (sensitivity 0.73, specificity 0.52), area under ROC curve was 0.63 (95% CI 0.55–0.72, $p = 0.007$) (Fig. 2).

CRP was also noted to have predictive value for severity of appendicitis. Recommended cut-off value for complicated/severe appendicitis was 28 (sensitivity 0.63, specificity 0.54), with an area under ROC curve at 0.61 (95% CI 0.51–0.70, $p = 0.027$) (Fig. 3).

Mann-Whitney testing demonstrated that a NLR cut-off value of 5.55 was a surrogate of increased overall LOS ($p < 0.0001$) between uncomplicated/simple and complicated/severe appendicitis. Additionally, there was a significant statistical difference between LOS for those with simple and severe appendicitis, with severe appendicitis resulting in a median of one extra in-patient day ($p < 0.0001$ Mann-Whitney test) (Fig. 4). Major 30-day post-operative complication rates were higher in the complicated/severe appendicitis group, with six patients (9%) being admitted versus nine patients (5.1%) in the uncomplicated/simple appendicitis cohort. Mean NLR was also statistically higher in those patients with post-operative complications (14.4 ± 2.4 for severe versus 9.3 ± 0.56 for simple appendicitis cohort, $p < 0.0001$) (Table 2 outlines the nature of major post-operative 30-day complications for each cohort). Comparison of retrospective and prospective values for NLR shows consistency in reported values with comparable sensitivity and specificity. 5.55 NLR cut-off value for uncomplicated/simple appendicitis is comparable to our previously reported value of 5.96; similarly, an NLR cut-off value of 6.35 for complicated/severe appendicitis in the current study is comparable to 6.36 in our retrospective series (Table 3).

Table 3 Comparison of NLR cut-off values in prospective and retrospective study

	NLR simple vs normal		NLR simple vs severe		CRP		LOS	Complication	Negative appendectomy
Retrospective	5.96		6.35		55.6		3.5	15	12.97%
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity			
	0.64	0.79	0.84	0.48	0.71	0.76			
Prospective	5.55		6.36		28		3.1	15	12.81%
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity			
	0.61	0.71	0.73	0.52	0.63	0.54			

Discussion

Appendicitis has traditionally been treated by appendectomy for more than a century. Recently, some have challenged this strategy proposing a conservative management approach [9]. Numerous publications have shown this practice to be both safe and efficacious [10–13, 28]. It is being postulated to consider an antibiotics-first strategy for uncomplicated appendicitis [14].

However, for a conservative management approach to be adopted, clinicians need to accurately identify patients with simple appendicitis and consider a trial of conservative management. Our retrospective study demonstrated that NLR has predictive ability of identifying severity of appendicitis and can also aid in identifying those needing urgent radiological assessment. To date, there has been limited prospective study to corroborate this.

This prospective study shows that NLR has a better area under the ROC curve (AUC, 0.74) compared to CRP (0.61) for predicting complicated/severe appendicitis and reasonable sensitivity and specificity. This suggests that NLR is a superior marker of acute phase response for inflammatory processes when compared to CRP, as pooled neutrophils in bone marrow are ready to react to acute inflammation. The response of CRP is delayed, because it is synthesized in liver in response to interleukin and cytokine pathway activation (IL-6) [17].

The accurate diagnosis of acute appendicitis and its severity can be elusive. Negative appendectomy rates of >20% have been reported in the past, but in recent years, this has reduced significantly [29, 30]. The use of biomarkers like NLR could further reduce this, while helping to delineate those requiring urgent surgery due to complicated/severe appendicitis.

This study also noted that NLR value predicts 30-days post-operative morbidity. It can be utilized to identify those patients that have increased risk of complications, and therefore, closer surveillance post-operatively should be considered. This study also supported that NLR is a surrogate of total length of stay. Those with complicated/severe appendicitis had a median of one extra in-patient day.

This paper validates findings of our previous publication [15]. However, we acknowledge the limitations of this study, mainly the lower number of patients, when compared with the retrospective series and lack of informative data regarding conversion to open procedure.

If the patients had been divided into simple or severe appendicitis on the basis of NLR values before intervention, it would have been interesting to see how the patients performed in their clinical outcomes in the two groups. Further studies are also needed to determine the outcome if patients are managed conservatively, on the basis of NLR cut-off values.

Additionally, several studies have shown that NLR is good biomarker in other inflammatory conditions like acute cholecystitis, diverticulitis, and inflammatory bowel disease [18, 19]. Its role is also being evaluated as a prognostic indicator in several visceral cancers [20–22].

Conclusion

NLR is a useful adjunct in predicting severity of appendicitis. It helps to delineate those patients with severe inflammation that should proceed to operative management, while indicating those for whom non-operative management may be considered. Furthermore, NLR is a surrogate marker of length of hospital stay and post-operative complication rates.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Addiss DG, Shaffer N, Fowler BS, Tauxe RV (1990) The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol 132(5):910–925
2. Rothrock SG, Pagane J (2000) Acute appendicitis in children: emergency department diagnosis and management. Ann Emerg Med 36(1):39–51
3. Storm-dickerson TL, Horattas MC (2003) What have we learned over the past 20 years about appendicitis in the elderly? Am J Surg 185(3):198–201
4. Waxman BP (2015) Treating uncomplicated appendicitis without surgery: will computer tomography scans and antibiotics triumph over clinical acumen and surgical dogma? ANZ J Surg 85(11):800
5. Chong CF, Adi MI, Thien A, Suyoi A, Mackie AJ, Tin AS et al (2010) Development of the RIPASA score: a new appendicitis scoring system for the diagnosis of acute appendicitis. Singap Med J 51: 22–225
6. Jang SO, Kim BS, Moon DJ (2008) Application of Alvarado score in patients with suspected appendicitis. Korean J Gastroenterol 52: 27–31
7. Bolger JC, Kelly ME, Barry K (2015) Acute appendicitis in the adult population: modelled decision analysis supports a conservative approach. J Gastrointest Surg 19(12):2249–2257
8. Roy H, Burbridge B (2015) To CT or not to CT? The influence of computed tomography on the diagnosis of appendicitis in obese pediatric patients. Can J Surg 58(3):181–187
9. Wilms IM, De Hoog DE, De Visser DC, Janzing HM (2011) Appendectomy versus antibiotic treatment for acute appendicitis. Cochrane Database Syst Rev 11:CD008359
10. Di Saverio S, Sibilio A, Giorgini E et al (2014) The NOTA study (non operative treatment for acute appendicitis): prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. Ann Surg 260(1):109–117

11. Foell D, Bahde R, Senninger N (2015) The non operative treatment for acute appendicitis (NOTA) study: is less surgery better surgery? Ann Surg 265(6):83–84
12. Rocha LL, Rossi FM, Pessoa CM, Campos FN, Pires CE, Steinman M (2015) Antibiotics alone versus appendectomy to treat uncomplicated acute appendicitis in adults: what do meta-analyses say? World J Emerg Surg 10:51
13. Vons C, Barry C, Maitre S et al (2011) Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. Lancet 377(9777):1573–1579
14. Ehlers AP, Talan DA, Moran GJ, Flum DR, Davidson GH (2016) Evidence for an antibiotics-first strategy for uncomplicated appendicitis in adults: a systematic review and gap analysis. J Am Coll Surg 222(3):309–314
15. Kelly ME, Khan A, Riaz M et al (2015) The utility of neutrophil-to-lymphocyte ratio as a severity predictor of acute appendicitis, length of hospital stay and postoperative complication rates. Dig Surg 32(6):459–463
16. Shimizu T, Ishizuka M, Kubota K (2015) A lower neutrophil to lymphocyte ratio is closely associated with catarrhal appendicitis versus severe appendicitis. Surg Today. doi:10.1007/s00595-015-1125-3
17. Heinrich PC, Castell JV, Andus T (1990) Interleukin-6 and the acute phase response. Biochem J 265:621–636
18. Posul E, Yilmaz B, Aktas G, Kurt M (2015) Does neutrophil-to-lymphocyte ratio predict active ulcerative colitis. Wien Klin Wochenschr. doi:10.1007/s00508-0140683
19. Kuon Lee S, Chul Lee S, Park JW, Kim SJ (2014) The utility of the pre-operative neutrophil-to-lymphocyte ratio in predicting severe cholecystitis: a retrospective cohort study. BMC Surg 14:100–107
20. Galizia G, Lieto E, Zamboli A, De Vita F, Castellano P, Romano C, Auricchio A, Cardella F, De Stefano L, Orditura M (2015) Neutrophil to lymphocyte ratio is a strong predictor of tumor recurrence: a propensity score-matched analysis. Surgery 158:112–120
21. Li MX, Lui XM, Zhang XF, Zhang JF, Wang WL, Zhu Y et al (2014) Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Int J Cancer 134:2403–2413
22. Yamanaka T, Matsumoto S, Termukai S, Ishiwata R, Nagai Y, Kukushima M (2007) The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. Oncology 73:215–220
23. Sevinç MM, Kınacı E, Çakar E et al (2016) Diagnostic value of basic laboratory parameters for simple and perforated acute appendicitis: an analysis of 3392 cases. Ulus Travma Acil Cerrahi Derg 22(2):155–162
24. Bayhan Z, Zeren S, Kargi E et al (2016) Does neutrophil to lymphocyte ratio predict hospital stay in appendectomy patients? Int Surg. doi:10.9738/INTSURG-D-15-00249.1
25. Yardımcı S, Uğurlu MÜ, Coşkun M, Attaallah W, Yeğen ŞC (2016) Neutrophil-lymphocyte ratio and mean platelet volume can be a predictor for severity of acute appendicitis. Ulus Travma Acil Cerrahi Derg. 22(2):163–168
26. Kucuk A, Erol MF, Senel S et al (2016) The role of neutrophil lymphocyte ratio to leverage the differential diagnosis of familial Mediterranean fever attack and acute appendicitis. Korean J Intern Med 31(2):386–391
27. Yazar FM, Bakacak M, Emre A et al (2015) Predictive role of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios for diagnosis of acute appendicitis during pregnancy. Kaohsiung J Med Sci 31(11):591–596
28. Hansson J, Körner U, Khorram-Manesh A et al (2009) Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. Br J Surg 96: 473–481
29. Seetahal SA, Bolorunduro OB, Sookdeo TC et al (2011) Negative appendectomy: a 10-year review of a nationally representative sample. Am J Surg 201(4):433–437
30. Talan DA, Saltzman DJ, Mower WR et al (2016) Antibiotics-first versus surgery for appendicitis: A US pilot randomized controlled trial allowing outpatient antibiotic management. Ann Emerg Med 70:1–11.e9