Original Research Article

A prospective study to assess the utility of neutrophil-to-lymphocyte ratio as a predictor of acute appendicitis

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Abstract
Acute appendicitis is one of the most common surgical emergencies in the world and has some well-known signs and symptoms, like increased leukocyte count and right lower quadrant pain. However, these predictors are not constant and their accuracy is questionable. Hence, it is necessary to improve the accuracy of diagnosis of acute appendicitis to prevent negative appendicectomies. In this study, we suggest that calculation of the NLR may provide a sensitive parameter in the preoperative prediction of AA and may help preoperatively to differentiate complicated from non-complicated appendicitis. A total of 108 patients who came with complaints of right iliac fossa pain and clinically diagnosed to have acute appendicitis were considered. Clinical diagnosis was established by means of history, physical examination, laboratory investigations and radiological investigations. In our study, it was noted 5.6% of the patients' histopathology showed a normal appendix, 59.3% showed acute uncomplicated appendicitis and 35.2% showed acute complicated appendicitis. NLR with a cutoff value of 3.17 was estimated to differentiate normal appendix and acute appendicitis with a sensitivity of 86.8% and specificity of 60%. The cut-off value for NLR to differentiate between acute appendicitis and acute complicated appendicitis was taken as 3.87, with a sensitivity of 84.2% and 63.9%.
Keywords: Neutrophil-to-lymphocyte ratio, predictor, acute appendicitis

Introduction
Acute appendicitis (AA) is one of the most common causes of acute abdomen. The lifetime occurrence of this disease is approximately 7%, with perforation rates of 17-20% [1].
The mortality risk is less than 1% in the general population, but can be around 50% in the elderly [2, 3]. As severe phlegmonous or gangrenous appendiceal inflammation can perforate and cause peritonitis, emergency surgery is imperative for patients with acute appendicitis. Thus, correct evaluation of acute appendicitis helps the surgeons in stratifying the severity of acute appendicitis. Although there have been recent advances in the management of appendicitis, surgery is still the first choice for treatment of acute appendicitis [4]. Despite imaging modalities and highly sensitive laboratory tests introduced into clinical use with the developing technology, diagnostic difficulties are still experienced and higher perforation

rates are encountered. The clinical diagnosis of appendicitis is mainly based on clinical history and physical findings.

However, in many published series, higher perforation (15-45%) and negative appendectomy (7-25%) rates demonstrate that despite evolving technological opportunities and clinical experience, a perfect diagnostic method has not yet been developed [5]. To supplement clinical diagnosis, laboratory investigations like TLC and CRP have been considered. The use of ultrasound (USG) for diagnosis has been widely accepted and studied. The Alvarado score and the Modified Alvarado score are used as diagnostic tools for acute appendicitis. However, up to date, there is no confirmatory laboratory marker for the diagnosis and prognosis of acute appendicitis.

In recent years, some researchers have reported on the predictive value of the neutrophil-to-lymphocyte ratio (NLR) for inflammation, which can be used as a diagnostic parameter in the perioperative diagnosis of acute appendicitis. Though there have been a few studies on NLR, all of them have reported that NLR appears to have greater diagnostic accuracy than traditional diagnostic laboratory tests (either white blood cell or C-reactive protein alone). It is also reported that NLR on admission to the hospital is an independent predictor of positive appendicitis histology [1].

NLR is simple to calculate and involves no additional cost, as it uses results from a standard complete blood count. The NLR is derived from the counts of circulating neutrophils and lymphocytes, both of which are major leukocyte populations. The inflammation triggered release of arachidonic acid metabolites and platelet activating factors results in neutrophilia and cortisol- induced stress results in relative lymphopenia, and thus, the NLR accurately represents the underlying inflammatory process [6].

In view of the above context, we suggest that NLR may provide a sensitive parameter in pre-op prediction of acute appendicitis and may help to differentiate complicated from non-complicated appendicitis. Complicated appendicitis included perforated and gangrenous appendicitis. NLR may also be used to prevent negative appendicectomies based on its predictive value [1].

Methodology
Inclusion criteria
All consecutive cases coming to the emergency department and OPD with a clinical diagnosis of acute appendicitis were considered. The diagnosis was confirmed with laboratory investigations and radiological investigations.

Exclusion criteria
Patients presenting 72 hours after the onset of abdominal pain.

Sample size
With the above criteria and with an absolute precision of 2% and with a desired confidence level of 95%, the sample size was 108 subjects.

Procedure
All patients who came to the Emergency Department and OPD of Ramaiah Hospital with complaints of right iliac fossa pain and diagnosed to have acute appendicitis were considered. The eligible patients were briefed about the nature of the study and a written informed consent was obtained. Thorough history was taken and clinical examination was done and was recorded on a predesigned and pretested pro forma. Clinical diagnosis was established by means of history, physical examination, laboratory investigations and radiological investigations.

Complete blood count which included hemoglobin%, total leukocyte count, differential leukocyte count and platelet count were all measured as a part of routine lab investigations. The absolute neutrophil and absolute lymphocyte count derived from the above investigations was calculated and neutrophil-to-lymphocyte Ratio (NLR) was derived from it.

The diagnosis post-operatively was confirmed with histopathological examination of acute appendicitis. Histopathological examinations of the appendix which showed gangrene, perforation and abscess were considered as acute complicated appendicitis.

Results

A total of 108 patients with a preoperative diagnosis of acute appendicitis were included in the study. The study had a male predominance with 74 men (68.5%) and 34 women (31.5%). The age range for patients in our study was observed to be between 11 and 80 years, with a median age of 27 years and a mean age +/- SD of 30.59 +/ 12.63 years. The most common age group in our study was 15- 25 (33.33%) and 25-35 (33.33%) years. In our study, all the 108 subjects underwent appendicectomy. 71 patients (65.74%) underwent laparoscopic surgery and 37 patients (34.26%) underwent open surgery. The demographic and clinical data have been reported in Table 1.

Table 1: Demographic Data

n=108

| Age	27
Male sex	74 (68.5)
Total leukocyte count (cells/mm3)	
<4,000	4 (3.70)
4,000-11,000	62 (57.41)
>11,000	42 (38.89)
Type of Surgery	
Laparoscopic	71 (65.74)
Open	37 (34.26)

Post-operatively, the diagnosis was confirmed with histopathology of the excised appendix. 6 patients (5.56%) showed normal appendix on histopathology, 64 patients (59.3%) showed acute uncomplicated (mild) and 38 patients (35.2%) showed acute complicated (severe) appendicitis (Graph 1).
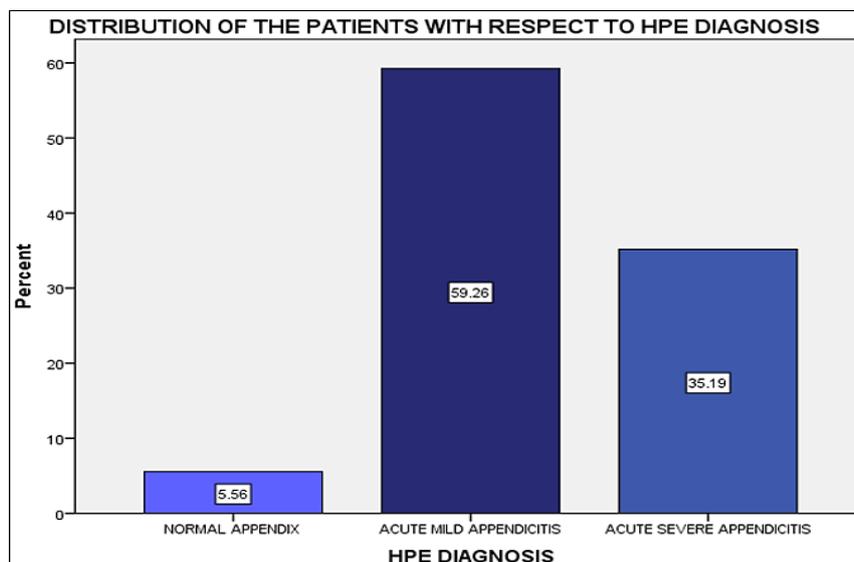
Graph 1

ROC curve for estimation of NLR

An ROC curve was constructed taking neutrophil-to-lymphocyte ratio against patients having acute appendicitis and negative appendicectomy. (Graph 2)
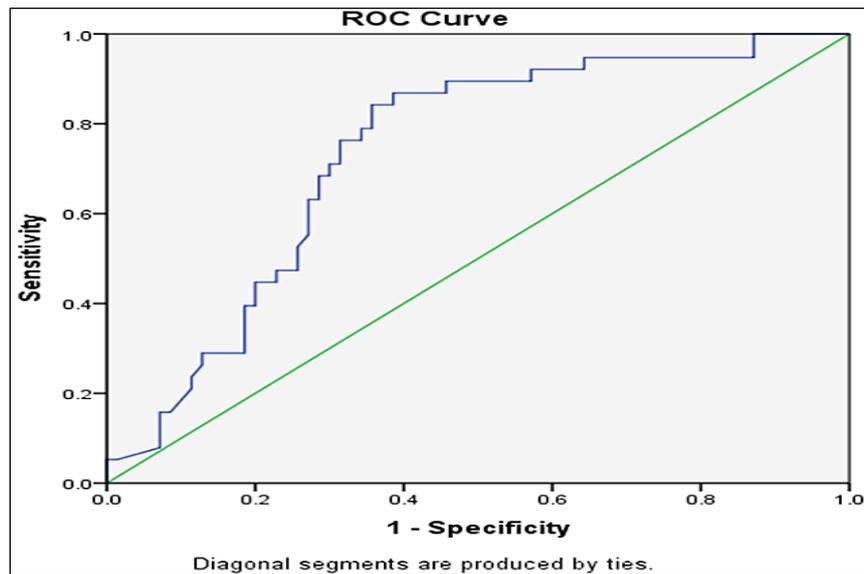
**Graph 2:** ROC Curve for NLR to Differentiate between Normal

Appendix and Acute appendicitis

After analyzing the co-ordinates, the best cut-off for the neutrophil-to-lymphocyte ratio to help us differentiate between normal appendix and acute appendicitis was determined as 3.1778 with a sensitivity of 86.8% and specificity of 60% with a p value of <0.001.
The area under the curve was 73.3% (AUROC).
The following co-ordinate was rounded off to the closest integer value of 3 and was taken as cut- off for the NLR ratio in predicting acute appendicitis.

NLR and Total leucocyte count
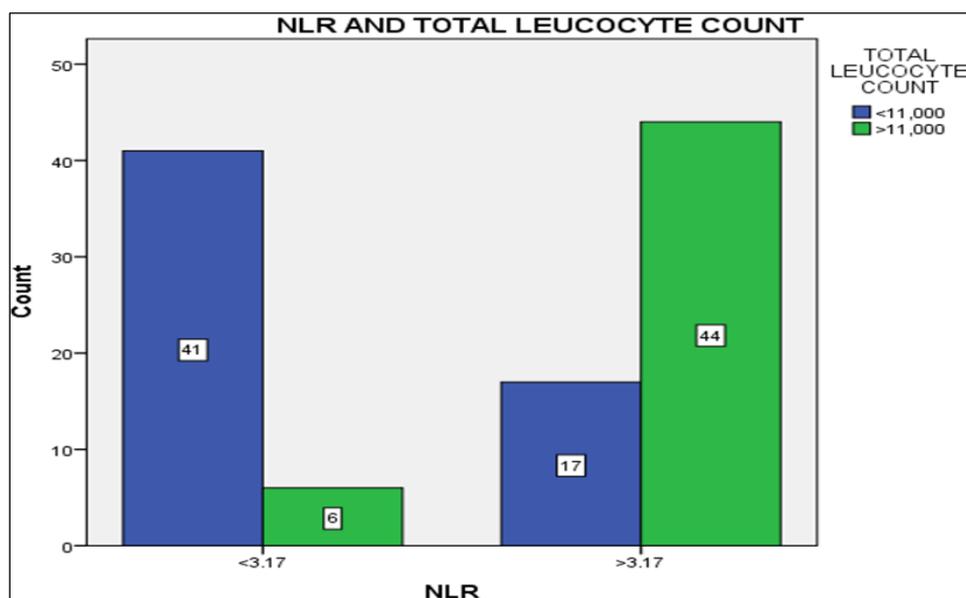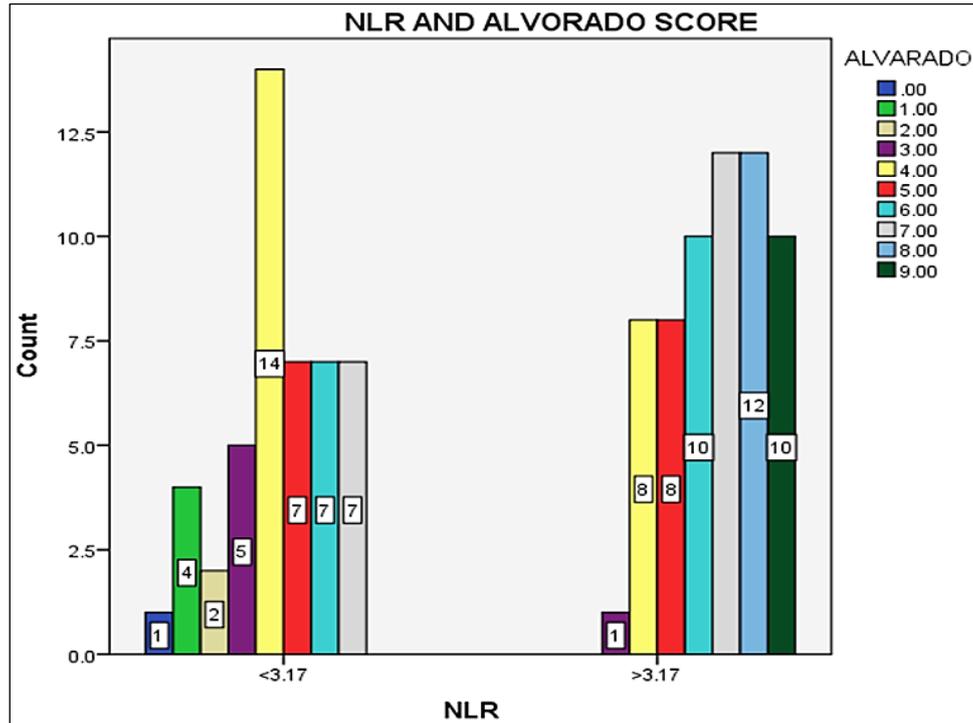

Graph 3

Graph 3 shows the distribution of patients with high and low TLC between the two groups (NLR<3.17 v/s NLR>3.17).

In this study, 87.2% of the patients with NLR<3.17 had TLC <11,000 cells/mm3 and 72.1% patients with NLR>3.17 had TLC >11,000 cells/mm3.

NLR and total leukocyte count association was found to be significant with p value <0.001.

Odds ratio was 17.68 → Patients with NLR>3.17 had 17.68 times the chances of having a TLC >11,000 cells/mm3 than those with NLR<3.17.

NLR and Alvarado score

Graph 4

Graph 4 shows the distribution of the patients in each group (NLR<3.17 v/s NLR >3.17) against their Alvarado's score.

It was seen that in patients with NLR<3.17, 29.4% of the patients had an Alvarado score of 4. In patients with NLR>3.17, 39.3% of the patients had an Alvarado score of 7-8. The association between NLR and Alvarado's score was statistically significant with p value <0.001.

ROC curve for estimation of NLR1

An ROC curve constructed taking neutrophil-to-lymphocyte ratio against patients suffering from acute uncomplicated and complicated appendicitis. This neutrophil-to-lymphocyte ratio was labeled as NLR1 (Graph 5).
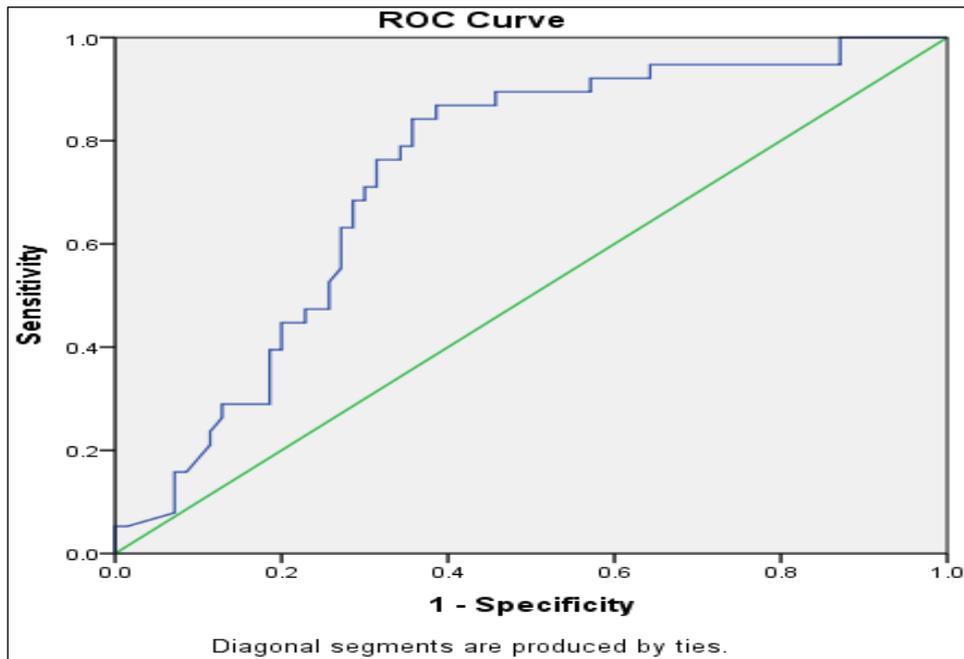
Graph 5: ROC Curve for Estimation of NLR1 to differentiate Between Acute Uncomplicated and Complicated Appendicitis

After analyzing the co-ordinates, the best cut-off to help us differentiate between acute complicated and acute uncomplicated appendicitis was determined as 3.8723 with a sensitivity of 84.2% and specificity of 63.9% with a p value of <0.001.
The area under the curve was 70%.
The following co-ordinate was rounded off to the closest integer value of 4 and was taken as cut-off for the NLR ratio in predicting the severity of acute appendicitis.

NLR1 and Severity of appendicitis
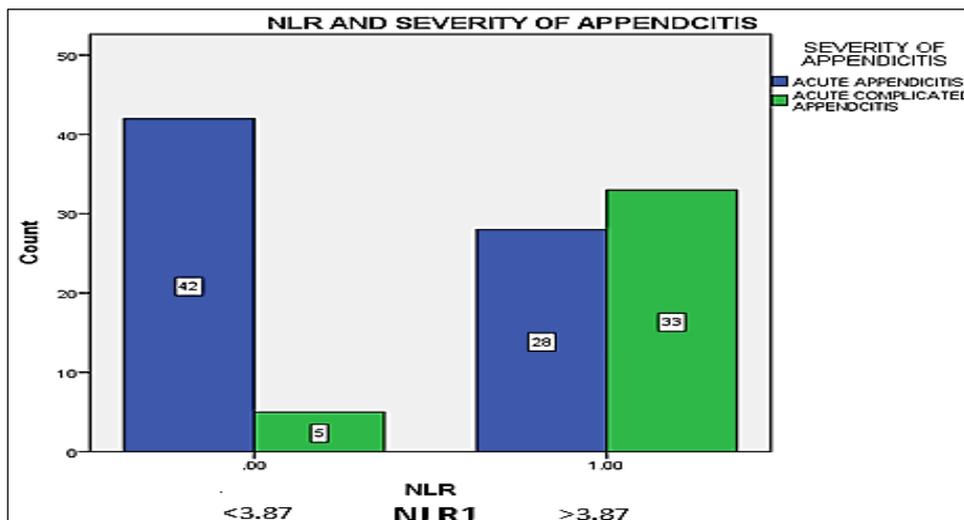
Graph 6: NLR1 and Severity of appendicitis

Graph 6 shows the distribution of patients with acute uncomplicated appendicitis and acute complicated appendicitis among both the groups (NLR1<3.87 v/s NLR1>3.87)
In our study, 89.3% of patients with NLR 1<3.87 had acute uncomplicated appendicitis and 54.3% of the patients with NLR1>3.87 had acute complicated appendicitis.
NLR and severity of appendicitis was significant with p value <0.001.

Odds ratio was 9.90→ a patient with NLR>3.87 has 9.9 times higher the risk of developing acute complicated appendicitis than those with NLR <3.87.
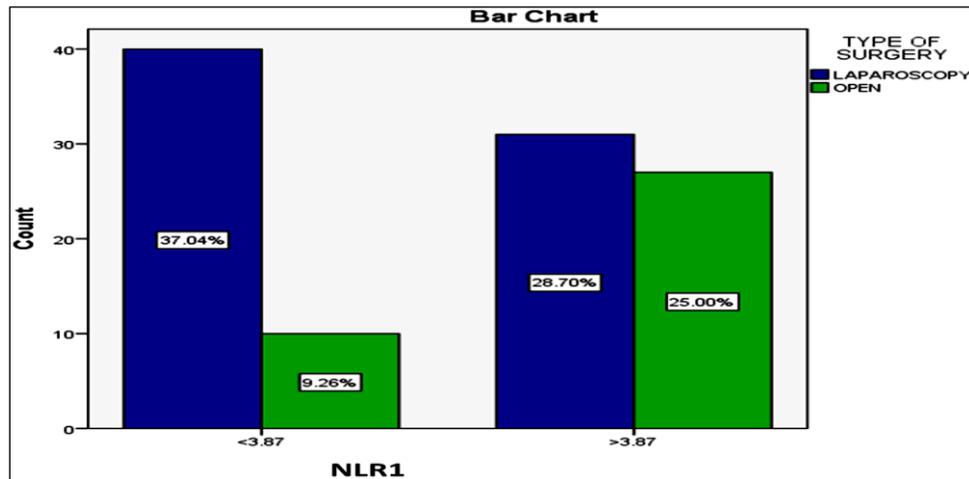
Graph 7: NLR1 and Type of surgery

Graph 7 shows the association between the distribution of the type of surgery between the two groups (NLR1<3.87 v/s NLR1>3.87)

In our study, 37.04% of the patients with NLR <3.87 underwent laparoscopic appendicectomy whereas 28.70% of the patients with NLR>3.87 underwent open appendicectomy.

NLR was found to be significantly associated with the type of surgery with a p value of 0.003. Odds ratio was 3.48 → patients with NLR>3.87 have 3.48 times greater the chances of undergoing open surgery than those with NLR 3.87.

Discussion

The diagnosis of acute appendicitis is critical as the decision to observe the patient until the diagnosis becomes obvious or to operate early to prevent unwanted complications like perforation and peritonitis represents a serious dilemma for surgeons.

An early operation may result in the removal of a normal appendix with a small risk of morbidity. Acute appendicitis is most likely an everyday occurrence in emergency units and requires distinct guidelines for diagnosis. The diagnosis is harder in rural areas where surgeons may not have imaging facilities. Radiological investigations are more sensitive but can delay the treatment. Thus, surgeons are still in need of an accurate and easy test to obtain the diagnosis. To overcome morbidity and mortality of perforation before surgery, a negative appendectomy is somewhat acceptable traditionally. However, in the recent years, many have considered this unacceptable and have studied means of improving the preoperative diagnosis [7, 8], since the operation itself is a cause of morbidity and mortality. In recent years, some authors reported that the neutrophil-to-lymphocyte ratio (NLR) is a predictor of inflammation and useful in the preoperative diagnosis of AA [9-11].

Though there have been a few studies on NLR, all of them have reported that NLR appears to have greater diagnostic accuracy than traditional diagnostic laboratory tests. NLR is simple to calculate and involves no additional cost, as it uses results from a standard complete blood count.

In this study, all the 108 patients underwent appendicectomy and the appendix was sent for histopathological examination. 5.6% of the patient's histopathology showed a normal appendix, 59.3% showed acute uncomplicated appendicitis and 35.2% showed acute complicated appendicitis. In the index study by Kahramanca *et al*., a normal appendix was seen in 15.9% patients, while acute uncomplicated and complicated appendicitis was seen in

70.6 and 13.4% patients respectively. Though the percentage of negative appendicectomies is lesser as compared to the positive appendicectomies, it is important to avoid negative appendicectomies.

65.74% and 35.26% patients underwent laparoscopic and open appendicectomies respectively. There was no incidence of conversion of laparoscopy to open surgery. Thus, this study shows that a majority of emergency appendicectomies can be operated laparoscopically.

For all the 108 patients who were clinically diagnosed to have appendicitis, blood samples were sent for the measurement of TLC. 4,000cells/mm3-11,000cells/mm3 was taken as the normal range. 57.41% patients had a TLC within the normal range, 38.89% of the patients had TLC >11,000cells/mm3 whereas 3.7% had a TLC>4,000 cells/mm3. TLC>11,000 cells/mm3 is considered as one of the diagnostic factors for acute appendicitis. However, in our study, majority of the patients with acute appendicitis had a normal TLC range.

In our study, NLR with a cutoff value of 3.17 was estimated to differentiate normal appendix and acute appendicitis. This NLR had a sensitivity of 86.8% and a specificity of 60%.

A study by Yazici *et al*. revealed that an NLR >3.5 has maximum sensitivity. They also indicated that higher N/L ratios have increased specificity and positive predictive value, while the most valuable results were obtained at NLR >5 [12]. In 2014, Kahramanca *et al*. published a study estimated the cut-off value of NLR as 4.68 to differentiate between normal appendix and inflamed appendix [1].

The acute appendicitis group was divided into complicated and non-complicated appendicitis and the cut-off value for NLR was estimated to be 5.74, with 70.8% sensitivity and 48.5% specificity. In limited number of published studies, a higher diagnostic value of NLR relative to conventional laboratory evaluations (leukocyte counts, C-reactive protein) has been indicated. In our study, NLR with a cutoff value of 3.17 was estimated to differentiate normal appendix and acute appendicitis. This NLR had a sensitivity of 86.8% and a specificity of 60%. Compared to the other studies, our study showed a NLR with a higher sensitivity and specificity.

In our study, on analyzing the NLR against the TLC, it was found to be significant ($p<0.001$) where 72.4% of the patients in with complicated appendicitis had a TLC>11,000cells/mm3 which is consistent with a study by Erkan et.al, wherein TLC was found to be significant ($p<0.001$) [13]. Alvarado's score used in the diagnosis of acute appendicitis was compared with NLR and was found to be significant ($p<0.001$) with higher Alvarado's scores corresponding to the higher cut-off value for NLR.

The cut-off value for NLR1 to differentiate between acute appendicitis and acute complicated appendicitis was taken as 3.87, with a sensitivity of 84.2% and 63.9%. The cut off value for complicated appendicitis was slightly higher than the NLR to predict acute appendicitis but the sensitivity and the specificity were almost similar. This data could have been so because of the low incidence of normal appendix in our study in comparison to the inflamed appendices. In the study by Ishizuka et.al, the cut-off value for gangrenous appendicitis was considered to be 8 and the values in our study were found to be much lower than that [4]. In the study of Yazici *et al*., it was reported that the sensitivity is maximum when NLR is >3.5, but specificity and PPV increase steadily when NLR increases and the most prominent values are reached when NLR is >5 [12]. As it is seen when cut-off value gets smaller it is more efficient to diagnose AA, when cut-off value gets bigger it is more efficient to diagnose non-sick patients.

In our study, 89.3% of patients with NLR1<3.87 had acute uncomplicated appendicitis and 54.3% of the patients with NLR1>3.87 had acute complicated appendicitis. NLR and severity of appendicitis was significant with p value<0.001. This reinforced that higher the NLR1, higher are the chances of the patient having complicated appendicitis.

In our study, 37.04% of the patients with NLR1 <3.87 underwent laparoscopic appendicectomy whereas 28.70% of the patients with NLR1>3.87 underwent open appendicectomy.

NLR was found to be significantly associated with the type of surgery with a p value of 0.003. This demonstrates that the surgical approach to acute appendicitis can be determined by NLR1>3.87, proving that complicated cases of acute appendicitis have a higher possibility of undergoing an open appendicectomy than laparoscopic appendicectomy.

Thus, in our study, we conclude that, preoperatively estimated NLR can be accepted as an easily available, affordable, adjunctive data as a factor in the diagnosis of acute appendicitis and also in predicting the severity of acute appendicitis.

Conclusion

In the present study, we conclude that preoperatively estimated NLR can be accepted as an easily available, affordable, adjunctive data as a factor in the diagnosis of acute appendicitis and also in predicting the severity of acute appendicitis. An NLR with a cut-off value of around 3.17 can be used in the diagnosis of acute appendicitis and an NLR of around 3.87 can be used to differentiate between acute uncomplicated and complicated appendicitis. Thus, NLR can be used as a useful tool for the diagnosis of appendicitis in those centers which have no all-time access to radiological investigations.

Conflict of interest: None.

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