

ORIGINAL RESEARCH ARTICLE

PREOPERATIVE NEUTROPHIL TO LYMPHOCYTE RATIO AS A PREDICTOR OF THE SEVERITY OF ACUTE APPENDICITIS

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**ABSTRACT**

**Background:** Neutrophil to lymphocyte ratio (NLR) is one of the tools to differentiate complicated and uncomplicated acute appendicitis (AA) preoperatively. However there is a considerable difference in the cutoff values of NLR in different studies. This study aimed to establish a cutoff value of NLR to distinguish complicated AA from uncomplicated AA preoperatively at our center.

**Methods:** This was a prospective observational study conducted over 2 years from January 2017 to December 2019 in the department of surgery, Chitwan Medical College Bharatpur. Patients with a provisional diagnosis of AA and undergoing appendectomy were included in the study. The difference in NLR between the two groups was compared by Mann-Whitney U-test. The predictive ability of NLR was estimated by the receiver operating characteristic (ROC) curve analysis.

**Results:** One hundred eighty-eight patients were included in the study, 112 patients were males and 76 were females. Among them, 29.2% (n=55) were complicated AA. Median NLR was significantly higher in the complicated AA group compared to the uncomplicated group (6.90 vs 4.27, P <0.001). On ROC analysis, the predictive ability of NLR for complicated AA was acceptable (AUC: 0.705, p <0.001). The optimal cut-off value of NLR to predict complicated acute appendicitis was 4.77, with sensitivity and specificity 74.5% and 65.4% respectively.

**Conclusions:** NLR  $\geq 4.77$  can be a useful adjunct in predicting complicated AA preoperatively. But because of poor sensitivity and specificity, a lower value does not exclude complicated AA, and therefore other biochemical and radiological parameters have to be taken into consideration.

**INTRODUCTION**

Appendectomy either by open or laparoscopic means has been the treatment of choice for patients with AA in most of the centers in the world.<sup>1-3</sup> Non-operative management has been practiced for uncomplicated AA in many centers<sup>4,5</sup>, but the pre-operative distinction between uncomplicated and complicated AA is very difficult. Neutrophil to lymphocyte ratio (NLR) has been suggested as one of the tools to differentiate complicated and uncomplicated AA preoperatively.

NLR is an inflammatory marker that has been used as a diagnostic and prognostic marker of various infective, inflammatory, and neoplastic diseases in the medical field.<sup>6</sup> Any physiological stress and pathological conditions cause an increase in the number of neutrophils and decrease the number of lymphocytes in the circulation, leading to altered NLR. This change in the immunological pattern after acute stress is attributed to cortisol and catecholamine release in the circulation.<sup>7</sup> A rise in NLR occurs in almost all the cases of AA and continues to increase in 85–95% of patients with complicated appendicitis.<sup>8</sup>

There is a considerable difference in the cutoff values of NLR to diagnose complicated AA in different studies. This variation could be due to the differences in the reference ranges indicated by different manufacturers'. Normal NLR also varies with ethnicity and geographical location.<sup>6</sup> Therefore, a local laboratory reference value should be established for the diagnosis and management of the disease. Therefore, we aimed to establish a cutoff value of NLR to distinguish complicated AA from uncomplicated AA preoperatively at our center.

**METHODS**

This was a prospective observational study conducted over 2 years from January 2017 to December 2019. All the patients with a provisional diagnosis of AA admitted in the surgical ward of Chitwan Medical College (CMC), Bharatpur, Nepal from January 2017 to December 2019 were studied. Ethical clearance was taken from CMC Institutional Review Board. Written informed consent was taken from all patients. Details of the patients were recorded in the pre-formed proforma that included patient demographics, laboratory tests, and radiological imaging (ultrasound) findings. For the analysis purpose, only the patients that underwent appendectomy and

had confirmed pathological diagnosis of AA were included. Patients diagnosed other than AA during surgery such as Colonic cancer, inflammatory bowel disease, and Ileo-cecal tuberculosis, histo-pathological normal appendix were excluded from the study.

Patients were divided into two groups: uncomplicated AA and complicated AA based on the guidelines provided by the World Society of Emergency Surgery.<sup>9</sup> Complicated AA refers to evidence of necrosis, phlegmon, abscess, or perforation whereas uncomplicated AA refers to a normal looking inflamed appendix during operation without any evidence of complication. All appendectomy specimens were sent for histopathological examination. Postoperatively patients were managed according to standard management protocol. NLR was calculated by dividing the absolute neutrophil count by absolute lymphocyte count, obtained from a complete blood count and a differential count. The data were analyzed using Statistical Package for Social Sciences (SPSS) for Windows version 26. Categorical variables were expressed as number (%). A Chi-squared test was used to compare proportions between the groups. The median NLR between the two groups was compared by using Mann-Whitney U-test. ROC curve analysis was used to analyze the preoperative predictive value NLR to differentiate complicated AA from uncomplicated AA. P-value <0.05 was considered clinically significant.

**RESULTS**

A total of 204 patients were admitted with a provisional diagnosis of AA during the study period. Histopathological examination (HPE) came out to be normal in 12 patients and 4 patients were diagnosed with appendicular neoplasm, and therefore were excluded from the study. The remaining 188 patients were included for further analysis.

Among them, 112 (59.57%) were males and 76 (40.42%) were females. The major bulk of AA was seen in young people below the age of 25 years (54.5%). Fifty five patients (29.2%) were complicated AA, with a ratio of uncomplicated to complicated AA is 2.4:1. Mean age of presentation was 25.29 with a standard deviation (SD) of 13.55 yrs. with an age range from 5-65 years. The incidence of complicated and uncomplicated AA in different age groups is shown in Table 1.

**Table 1: Incidence of complicated and uncomplicated AA in different age groups**

Age (years)	Uncomplicated AA (n=133)	Complicated AA (n=55)
5-15	42 (31.57%)	9 (16.36%)
16-25	36 (27%)	15 (27.27%)
26-35	28 (21%)	18 (32.72%)
36-45	16 (12%)	4 (7.27%)
46-55	8 (6%)	7 (12.72%)
56-65	3 (2.25)	2 (3.63%)

There was a higher incidence of complicated AA seen in male patients (67.27% (n=37) vs. 32.72% (n=18). There was no dif-

ference in the incidence of complicated AA and the duration of symptoms (Table 2).

**Table 2: Duration of symptoms and complicated AA**

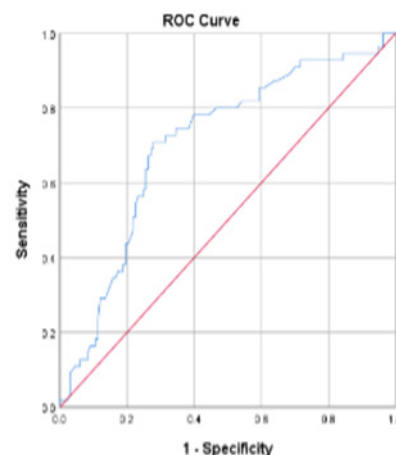
Duration of symptoms (hours)	Uncomplicated (n=133)	Complicated (n=55)
<12	24 (18%)	10 (18.18%)
12-24	47 (35.33%)	18 (32.72%)
> 24	62 (46.61%)	27 (49%)

Leucocyte count was also in a higher range in complicated AA. Sixty-one percent of patients with complicated AA had more than 12000/cumm, whereas in uncomplicated cases it was 48.1%.

A higher value of Neutrophil to lymphocyte ratio (NLR) was observed in patients with complicated AA as compared to uncomplicated AA. For complicated AA, the median NLR was 6.90 (1.36-46), whereas, for uncomplicated AA, NLR was 4.27 (0.80-31.60 p <0.001). On ROC analysis, the predictive ability of NLR for the detection of complicated AA was within acceptable range with an area under curve 0.705 p<0.001. The optimum value of NLR to predict complicated AA was 4.77 with sensitivity and specificity 74.5% and 65.4% respectively (Figure 1). Sensitivity and specificity of NLR at a different cut-off value are shown in Table 3.

**Table 3: Sensitivity and specificity of NLR at a different cut-off value**

NLR	Sensitivity (%)	Specificity (%)
2	94.5	9
4	81.8	45
6	58.2	76
8	36.4	82
10	16.4	91



**Figure 1: ROC curve for complicated and non-complicated appendectomies. The area under the ROC curve: 0.705 95% CI p-value <0.001.**

The median duration of hospital stay was 3 days and 6% showed normal appendix on histopathology examination.

## DISCUSSION

Diagnosis of AA is still based on clinical judgments.<sup>10</sup> Several scoring systems have been developed and used by the clinician to help in the diagnosis of AA.<sup>11,12</sup>

The decision whether to operate or manage conservatively, especially for non-complicated AA is of concern in the management of the patient especially in the western world these days.<sup>13,14</sup> Open appendectomy has been the gold standard for the treatment of AA in the past, whereas, in these days, a laparoscopic approach is equally safe and effective over open method with shorter duration of hospital stay, decreased post-operative pain and low incidence of post-operative wound infection.<sup>13,15</sup>

In an advanced setup, a CT scan is commonly done not only for the diagnosis of AA but also for the detection of complications.<sup>16</sup> It not only prevents negative appendectomy rates but also prevents extra costs and complications associated with operation. However, in a resource-constrained setting where CT scan is not easily available, when patients cannot afford the cost of CT scan and ultrasound reports are inconclusive, only clinical examination or scoring systems derived from clinical examination and laboratory investigations help in decision-making, timely management, and the referral. NLR is regarded as one of the simplest tools to diagnose AA in patients with right iliac fossa pain and differentiate it from complicated AA.<sup>17</sup> It can be easily derived from a simple routinely done blood investigation (i.e. complete blood count and differential count), helping in decision-making and prioritizing the cases for early surgery with a higher risk of perforation.

Obstruction of the lumen of the appendix by fecolith is the main causative factor for the complications in AA, which is responsible for the perforation in about 90% of cases.<sup>18</sup> Literature also shows a higher incidence of perforation in males compared to females,<sup>19,21</sup> that is also observed in our study. The reason, although not well explained, is believed that male patients can tolerate pain better than female patients and reluctant to go to the hospital.<sup>21</sup> The role of the sex hormones in the pathogenesis of AA is well established, but its role in perforation has not been established yet.<sup>22,23</sup>

The incidence of complicated AA varies in different literature and can reach up to 60%.<sup>24</sup> Pedziwiatr M et al and Atema JJ et al in their studies showed the incidence of complicated AA to be around 28%, similar to our study.<sup>25</sup> Similarly, Khan MS et al had

reported an incidence of 20% for complicated appendicitis.<sup>26</sup> A higher value of Neutrophil to Lymphocyte ratio (NLR) has been observed in complicated AA in most of the literature, with variable cut-off values. A study done by Kelly ME et al in 663 patients showed an NLR of >6.35 associated with severe AA with a sensitivity of 84.9% and specificity of 48.2%.<sup>27</sup> Kahraman S et al reported an NLR of 5.74 to be associated with complicated AA.<sup>28</sup> Similarly, in a study done by Ishizuka M et al, NLR of > 8 shows good association with gangrenous AA with sensitivity 73% and specificity 39%, respectively.<sup>29</sup> In a systemic review and meta-analysis done by Hajibandeh S et al, NLR was suggested to be a simple preoperative marker to differentiate between complicated and simple AA, with an optimal cut-off of 8.8 with a sensitivity of 76.92% and specificity of 100% with AUC of 0.91.<sup>17</sup> In our study also, NLR had only acceptable predictive ability (not good or excellent).

In the present study, though NLR value was a higher range in complicated AA and the predictive ability of NLR for the detection of complicated AA was acceptable range (area under curve 0.705,  $p < 0.001$ ) with poor sensitivity and specificity (74.5% and 65.4% respectively).

One of the major limitations of our study is there is a wide range of variations in normal NLR in a different group of the population, different ethnicity, and geographical location.<sup>6,30,31</sup> This variation in normal cut off value could be due to the difference in reference ranges indicated by different manufacturers and different laboratory machines have different measuring principles. Therefore local laboratory reference values should be established<sup>30</sup> so that this can be applied in the diagnosis and management of the disease.

## CONCLUSION

NLR  $\geq 4.77$  can be a useful adjunct in predicting complicated AA preoperatively, with poor sensitivity and specificity however, a lower value does not exclude the diagnosis, and other biochemical and radiological parameters have to take into consideration to confirm it. To find optimal NLR and its accuracy, further prospective randomized studies are needed and local laboratory reference values should be established so that this can be applied in the diagnosis and management of a disease.

**CONFLICT OF INTEREST:** None

**FINANCIAL DISCLOSURE:** None

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