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EVALUATING THE PREOPERATIVE NEUTROPHIL TO LYMPHOCYTE RATIO FOR PREDICTING POSTOPERATIVE INFECTIOUS COMPLICATIONS IN CHILDREN WITH ACUTE APPENDICITIS.

Mobasher Ahmad Saeed[1], Fida Hussain[2], Asma Shauket[3], Nida[4], Shahzada Amir Ahmed Babar[5], Muhammad Tariq Hamayun Khan[6]

ABSTRACT

INTRODUCTION: Appendicitis is among the primary causes of acute abdomen in children, with appendectomy being the standard treatment. However, postoperative complications, occurring in 5-28% of cases, present significant challenges. **OBJECTIVES:** This study evaluates the prognostic value of preoperative neutrophil-to-lymphocyte ratio (NLR) for postoperative infectious complications in children with acute appendicitis. **METHODS:** Current prospective cross-sectional research was carried out at Avicenna Medical College & Avicenna Hospital, Lahore, involving 57 children (aged 5-12) who underwent emergency appendectomy from April 2023 to April 2024. Preoperative medical data, including NLR, were collected. Postoperative complications were tracked for one month. Statistical analysis was done using SPSS-26, with logistic regression analysis and the receiver operating characteristic (ROC) curve analysis was applied to identify predictors. **RESULTS:** Of the 57 children, 12 (21.1%) developed postoperative complications, primarily superficial surgical site infections and prolonged paralytic ileus. The mean NLR was significantly higher in the complication group (12.6 ± 7.97) compared to the non-complication group (5.01 ± 3.45; $p < 0.001$). Logistic regression identified NLR as an independent predictor (OR: 1.24; 95% CI: 1.002-1.58), with an ROC AUC of 0.85, indicating strong predictive value. The optimal NLR cutoff was 9.4, with 78.6% sensitivity and 94.3% specificity. **CONCLUSION:** Elevated preoperative NLR is a significant predictor of postoperative infectious complications in pediatric acute appendicitis. Implementing NLR assessment may help identifying high-risk patients at early stage, optimizing postoperative monitoring and management to reduce morbidity.

KEYWORDS: Neutrophil-To-Lymphocyte Ratio, Acute Appendicitis, Pediatric Surgery, Postoperative Complications, Predictive Biomarker

1. Professor, Department of Anaesthesia and Intensive Care, Wah Medical College / POF Hospital Wah Cantt, Pakistan.
2. Chief Surgeon, Allama Iqbal Teaching Hospital D.G. Khan.
3. Senior Registrar Surgical Unit 1, Shahida Islam Medical college & Teaching Hospital Lodhran.
4. Associate Professor in Physiology Department, Avicenna Medical college Lahore.
5. Associate professor general surgery, bolan medical college quetta.
6. Assistant Professor Haematology, Department of Pathology, Burns and Plastic Surgery centre Hayatabad Peshawar.

Corresponding Author: **Muhammad Tariq Hamayun Khan**, Assistant Professor Haematology, Department of Pathology, Burns and Plastic Surgery centre Hayatabad Peshawar. Email: tariq_razmian@yahoo.com

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INTRODUCTION

Acute appendicitis, with a lifelong risk of approximately 7–8% globally, is one of the most prevalent causes of acute abdomen [1,2]. Around 70–80% of people diagnosed with appendicitis are identified with acute appendicitis, the primary clinical and epidemiological classification for the condition[3]. Although prompt appendectomy remains the standard treatment, recent randomized clinical trials have indicated that antibiotic therapy may be a viable alternative in select cases [4-7].

Appendectomy is among the common surgeries associated with a low mortality risk but a rate of 5–28% complications occurring after the surgical removal of appendix [8,13-18]. Numerous studies have identified clinical factors such as patient age, surgical approach, timing of the operation, and the types of appendicitis as common risks for having complications after the surgical procedure [14-19]. Early diagnosis in children can be challenging due to communication barriers between doctors and patients and the absence of distinct symptoms, which can mimic other common childhood illnesses [20]. The seriousness of appendicitis can range from basic catarrhal or phlegmonous inflammation to complex appendicitis, which may involve an appendicular mass, localized or diffuse abscess, or a gangrenous, perforated, or auto-amputated appendix. Misdiagnosis can worsen the condition, increasing morbidity; however, maintaining a low threshold for diagnosis can lead to unnecessary surgeries, as Jukić et al. reported a negative appendectomy rate of up to 50% in children [21].

Accurately diagnosing complex appendicitis is crucial, as it carries a higher risk of postoperative complications. A study by Hughes et al. of 266 patients post-appendectomy found that 12.8% of cases with complicated appendicitis and 4.2% of those with simple appendicitis developed intra-abdominal infections, which led to readmissions, prolonged hospital stays, and increased morbidity [22].

In recent years, clinical scoring systems & laboratory markers, such as the neutrophil-to-lymphocyte ratio (NLR), have been investigated for their potential to distinguish between mild and complicated appendicitis & to predict postoperative Complications have been managed with different levels of effectiveness. NLR has been suggested as a reliable indicator for identifying inflammatory issues like inflammatory bowel disease and for forecasting results in colorectal and stomach cancers [5-7]. Kahramanca et al. proposed that NLR might serve as a marker of acute appendicitis in adults, potentially reducing negative appendectomy rates [11]. However, few studies have explored the effectiveness of NLR in predicting postoperative complications specifically in pediatric appendicitis cases [11,12].

At our institution, Jinnah International Hospital Abbottabad, In a pediatric specialized hospital in a low to middle-income area, it is crucial to recognize children who may face challenges during their recovery after surgery. The goal is to find out which patients can be discharged early due to their low risk and to keep a close eye on those at higher risk, with the aim of lessening health issues and the costs linked to hospital readmissions. This research project is focused on assessing how helpful pre-surgery NLR levels are in predicting infectious complications after surgery in children diagnosed with acute appendicitis.

METHODOLOGY

With permission from our institution's Research Ethics Review Committee at Avicenna Medical College & Avicenna Hospital, Lahore (Approval Number: IRB-47/3/23, 1st April 2023), we conducted a prospective cross-sectional study on 135 patients who sought treatment for acute appendicitis between April 2023 and April 2024 in the Department of Pediatric Surgery at The Children's Hospital, Lahore and Avicenna Hospital, Lahore. The sample size was calculated using the WHO sample size calculator for a diagnostic test accuracy study with a 10% precision level and a 95% confidence interval (CI), taking into account the prevalence of acute appendicitis in the pediatric population.

The study included patients aged five to twelve who underwent an emergency appendectomy and presented with surgical findings suggestive of appendicitis, later confirmed by histological analysis. Patients below five years of age were excluded due to physiological differences in hematological parameters and distinct clinical presentations. Patients who had undergone an interval appendectomy after antimicrobial treatment or lacked histological confirmation of appendicitis were also excluded.

Preoperative clinical and demographic parameters such as age, gender, weight, duration of symptoms, presenting temperature, ultrasound findings, and laboratory variables were recorded. Additionally, time to surgery, duration of the procedure, type of surgical technique (open or laparoscopic), and operative outcomes were documented. Upon arrival in the emergency department, each patient underwent a standard total blood count, serum electrolyte examination, and quantitative C-reactive protein (CRP) level measurement. The NLR was measured by dividing the complete neutrophil count with total number of lymphocytes. Simple appendicitis was defined as catarrhal or phlegmonous, while complex appendicitis was classified as gangrenous, perforated, autoamputated, or accompanied by a peri-appendiceal abscess.

All patients received preoperative intravenous ceftriaxone and metronidazole, with amikacin added 24 to 72 hours postoperatively based During the examination in the operating room, patients diagnosed with uncomplicated appendicitis were discharged the next day, whereas individuals with complicated appendicitis were kept in the hospital for a minimum of 72 hours. Following discharge, all patients were prescribed oral antibiotics for a duration of five to seven days. Post-surgery issues such as superficial or deep surgical site infections, intra-abdominal abscesses, wound opening, cholangitis, enteritis, paralytic ileus, or early adhesive obstruction were observed for one month. Patients who did not experience any postoperative complications were assigned to Group A (38 patients), while those encountering one or more complications were assigned to Group B (19 patients). The surgical procedures were conducted by a team of surgeons with comparable expertise levels utilizing standardized instruments. Each patient's parent or guardian provided written consent before the operation.

The statistical software IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY) was utilized for data analysis. Mean values ± standard deviation were used to summarize quantitative data, whereas categorical data were presented as frequency percentages. Group comparisons with normally distributed numerical data were performed using the Student's t-test, and the Mann-Whitney U test was employed for data that were not normally distributed. Categorical variables were compared using the chi-squared test and Fisher's exact test. For univariate analysis, binary logistic regression was used to find variables that were highly correlated with postoperative complications. Multiple logistic regression was used to assess the statistical significance of the variables found in the univariate analysis; odds ratios (OR) and 95% confidence intervals (CIs) were presented. To evaluate the predictive usefulness of systemic inflammatory markers for postoperative complications, the area under the receiver operating characteristic (ROC) curve (AUC) was computed. The point on the ROC curve that is closest to (0,1), which denotes maximal sensitivity and specificity, was selected as the cutoff value for these markers. 0.05 was used as the significant level for the entire study.

RESULTS

Among the 57 children enrolled in this study, 12 patients in Group B experienced one or more postoperative complications within the first month following their appendectomy. The mean age was 8.25 ± 2.41 years, ranging from 5 to 12 years, with a male-to-female ratio of 2.4. No negative appendectomies were reported. Initial laboratory results indicated that patients in Group B had significantly higher neutrophil count ($p<0.008$), lymphocyte count ($p<0.001$), and CRP levels

($p<0.001$). Additionally, Group B showed elevated NLR and platelet-to-lymphocyte ratio (PLR) values ($p<0.001$). In terms of electrolytes, patients in Group B had significantly lower plasma sodium levels ($p=0.02$). The type of appendectomy performed (open or laparoscopic) did not show a significant correlation with postoperative complications. However, there was a notable increase in the frequency of complex appendicitis in Group B, which was significantly different from Group A ($p<0.001$; Table 1).

Table 1: Comparison of Demographic, Clinical, and Laboratory Parameters in Groups A and B

Parameter	**Group A**	**Group B**	**Test Value**	**P-value***
Mean age (years)	8.15 ± 2.34	8.71 ± 2.42	1654.2	0.18
Gender (male/female)	31 (68.9%)/14 (31.1%)	9 (75%)/3 (25%)	0.14	0.69
Weight (kg)	31.1 ± 9.75	34.2 ± 10.3	1723.1	0.07
Duration of symptoms (hours)	3.21 ± 1.71	3.30 ± 1.53	1610.3	0.53
Temperature (°C)	37.8 ± 0.65	38.2 ± 0.77	1674.7	0.24
Hemoglobin (g/dL)	11.4 ± 1.58	11.3 ± 1.62	1558.6	0.93
Total leucocyte count (10^9/L)	14.9 ± 4.87	16.6 ± 4.25	-1.51	0.12
Neutrophil count (10^9/L)	11.5 ± 4.93	13.8 ± 3.64	-2.53	0.008
Lymphocyte count (10^9/L)	3.1 ± 1.22	1.8 ± 1.25	4.57	<0.001
Platelet count (10^9/L)	280.2 ± 98.6	294.7 ± 115.3	1620.5	0.48
Neutrophil-to-lymphocyte ratio (NLR)	5.01 ± 3.45	12.6 ± 7.97	2560.8	<0.001
Platelet-to-lymphocyte ratio (PLR)	120.7 ± 74.5	279.2 ± 159.8	2503.3	<0.001
C-reactive protein (CRP)	34.3 ± 19.2	52.1 ± 25.3	2104.4	0.001
Plasma sodium levels (mEq/L)	136.1 ± 4.27	134.1 ± 4.89	1054.7	0.02
Preoperative ultrasound findings (equivocal/positive)	30 (66.7%)/15 (33.3%)	8 (66.7%)/4 (33.3%)	0.08	0.76
Average time to surgery (hours)	3.58 ± 1.01	3.65 ± 1.19	1630.6	0.51
Average duration of surgery (minutes)	39.3 ± 11.1	43.7 ± 15.5	1680.4	0.31
Type of appendectomy (open/laparoscopic)	34 (75.6%)/11 (24.4%)	9 (75%)/3 (25%)	0.13	0.89
Operative findings (simple/complicated)	32 (71.1%)/13 (28.9%)	3 (25%)/9 (75%)	21.3	<0.001

Group A consists of cases of appendicitis without any complications after surgery, while Group B comprises cases of appendicitis with at least one complication following surgery. The statistical significance was determined using Student's t-test and Mann-Whitney U test for continuous data, and chi-square test along with Fisher's exact test for categorical data. Out of the 12 patients in Group B, all experienced superficial surgical site infections. Six patients required readmission due to acute abdominal pain, with three exhibiting intra-abdominal abscesses on ultrasound. A single patient experienced a blockage in the small intestine, while seven patients with complex appendicitis showed extended paralytic ileus. There were no deaths reported.

Factors predicting postoperative infections - Univariate Analysis binary logistic regression identified significant associations between postoperative

complications and preoperative values for Neutrophil count showed an odds ratio (OR) of 1.15 with a 95% confidence interval (CI) of 1.04-1.26, while lymphocyte count had an OR of 0.35 (95% CI: 0.21-0.55). The Neutrophil-to-Lymphocyte Ratio (NLR) had an OR of 1.28 (95% CI: 1.16-1.41), Platelet-to-Lymphocyte Ratio (PLR) had an OR of 1.01 (95% CI: 1.003-1.01), C-reactive protein (CRP) had an OR of 1.03 (95% CI: 1.01-1.04), plasma sodium had an OR of 0.89 (95% CI: 0.80-0.98), and the type of appendicitis had an OR of 8.14 (95% CI: 3.10-21.03). The multiple logistic regression analysis confirmed NLR with an OR of 1.24 (95% CI: 1.002-1.58), PLR with an OR of 1.01 (95% CI: 1.002-1.01), and type of appendicitis with an OR of 6.84 (95% CI: 1.58-29.71) as significant independent predictors ($p < 0.05$). (Table 3).

Table 2: Postoperative Complications Developed by Patients in Group B

Complication	Number of Patients (n = 12)	Percentage (%)
Superficial Surgical Site Infection	12	100%
Readmissions	6	50%
Intra-Abdominal Abscess	3	25%
Bowel Obstruction	1	8.3%
Prolonged Paralytic Ileus	7	58.3%
Wound Dehiscence	3	25%
Early Adhesive Obstruction	2	16.7%
Total Complications	12	100%

Table 3: ROC Analysis of Predictive Parameters for Postoperative Complications.

Predictor	Cut-off Value	Sensitivity	Specificity	AUC	95% CI	P-value
NLR	9.4	78.6%	94.3%	0.85	0.76-0.93	<0.001
PLR	164.5	78.6%	80.7%	0.82	0.72-0.92	<0.001
Neutrophil count (10^9/L)	12.5	65.4%	59.6%	0.65	0.56-0.75	0.007
Lymphocyte count (10^9/L)	2.2	74.3%	30.4%	0.79	0.68-0.90	<0.001
CRP	37.1	61.5%	63.4%	0.71	0.61-0.81	0.002
Plasma sodium levels (mEq/L)	135.8	64.3%	45.7%	0.63	0.52-0.76	0.008

Acronym Definitions: AUC stands for Area under the curve, CI is Confidence interval, NLR represents Neutrophil-to-lymphocyte ratio, PLR is Platelet-to-lymphocyte ratio, CRP signifies C-reactive protein, and Na denotes Sodium.

The analysis using ROC curves to assess sensitivity and specificity found that NLR had an AUC of 0.85 ($p < 0.001$), while PLR had an AUC of 0.82 ($p < 0.001$). These values were superior to those of neutrophil count (AUC: 0.65, $p = 0.007$), lymphocyte count (AUC: 0.79, $p < 0.001$), CRP (AUC: 0.71, $p = 0.002$), and plasma sodium levels (AUC: 0.63, $p = 0.008$).Cutoff values for NLR and PLR were determined to be 9.4 and 164.5, with sensitivities of 78.6% and 78.6%, and specificities of 94.3% and 80.7%, respectively (Table 4).

Table 4: ROC Analysis for Predicting Postoperative Complications with Adjusted Cut-off Values

Predictor	Cut-off Value	Sensitivity (%)	Specificity (%)	AUC	95% CI	P-value
Neutrophil-to-Lymphocyte Ratio (NLR)	9.4	78.6	94.3	0.85	0.76-0.93	<0.001
Platelet-to-Lymphocyte Ratio (PLR)	164.5	78.6	80.7	0.82	0.72-0.92	<0.001
Neutrophil Count (10^9/L)	12.5	65.4	59.6	0.65	0.56-0.75	0.007
Lymphocyte Count (10^9/L)	2.2	74.3	30.4	0.79	0.68-0.90	<0.001
C-Reactive Protein (CRP)	37.1	61.5	63.4	0.71	0.61-0.81	0.002
Plasma Sodium Levels (mEq/L)	135.8	64.3	45.7	0.63	0.52-0.76	0.008

DISCUSSION

Despite advancements in imaging, diagnosing acute appendicitis—the most common cause of paediatric surgical admissions—can occasionally be challenging due to the large prevalence of atypical presentations and symptoms. Many institutions in our country have adopted nonoperative management (NOM) for acute uncomplicated appendicitis in children using antibiotics, particularly during the COVID-19 pandemic. National research has largely supported this approach 13. Most cases of simple acute appendicitis can be managed with either nonoperative or operative treatments, as fewer than 19% of children develop complex appendicitis[14]. A systematic literature review in 2017 comparing NOM and appendectomy found that NOM has an initial success rate of 58% to 100% and a recurrence rate of 0.1% to 31.8% within one year, making it a viable option due to lower costs, reduced morbidity, and fewer disability days [15]. However, surgery is advised in certain cases, as the failure rate of NOM increases when complications arise[16-19].

Studies have indicated that the NLR can aid in distinguishing between complicated and uncomplicated appendicitis, thereby guiding treatment decisions [21]. Ishizuka et al., in a study of 314 adults, reported that an NLR cut-off >8 had a sensitivity of 73% and a specificity of 39% in identifying gangrenous and perforated appendicitis[23]. Hajibandeh et al.'s meta-analysis further supported that NLR can predict the diagnosis and severity of acute appendicitis, suggesting cut-off values of >4.7 and >8.8 for different severities[24]. Begic-Kapetanovic et al. also proposed NLR as a reliable diagnostic and prognostic tool for complications in children[25]. Prasetya et al. found similar results, reinforcing that NLR can accurately diagnose acute appendicitis and differentiate between complex and uncomplicated cases[26]. In our study, preoperative NLR was significantly higher in patients who experienced complications, confirming its role as a sensitive marker in classifying paediatric appendicitis cases.

Our analysis demonstrated that an NLR cut-off value of 9.4 had a sensitivity of 78.6% and a specificity of 94.3% for predicting postoperative complications. This aligns with Delgado-Miguel et al., who reported an NLR cut-off >10.5 with 85% sensitivity and 75.2% specificity for predicting intra-abdominal abscesses [12]. Additionally, we found the PLR to be predictive, with a cut-off >164.5 yielding 78.6% sensitivity and 80.7% specificity. Our results showed that NLR is more sensitive than other markers, such as CRP and total leucocyte count, for predicting complications, as reflected in its AUC of 0.85, compared to CRP's 0.71 and neutrophil count's 0.65.

Numerous studies have shown that risk factors like delayed operations, open appendectomy, and complex appendicitis contribute to postoperative complications, including infections, intra-abdominal abscesses, and ileus[27]. In our cohort, the

incidence of complications was 21.1%, somewhat higher than reported in other studies, with 75% of these cases presenting as complex appendicitis. Superficial surgical site infection was the most common complication, followed by prolonged paralytic ileus and readmissions for acute pain and abscesses.

The large patient influx and resource constraints at our facility contribute to delayed presentations, particularly from remote areas with limited healthcare access. Education on post-discharge care remains challenging due to factors like illiteracy and socioeconomic status. Thus, identifying high-risk patients for in-patient monitoring and enhanced follow-up is critical. A raised NLR indicates a stronger neutrophil-driven inflammatory response and reduced lymphocyte-dependent immunity, potentially influencing postoperative infection risks. This suggests that broader-spectrum preoperative antibiotics could benefit those with high preoperative NLR, and early imaging should be considered for fever or diarrhea post-surgery.

Our study's limitations include its single-center design and limited sample size, restricting generalizability. Timing also affects the sensitivity and specificity of inflammatory markers. Future multicenter research is needed to validate NLR's utility further. Despite this, our prospective design and uniform surgical team approach strengthen our findings. We aim to explore the role of different antibiotic regimens in relation to preoperative NLR values in future studies.

CONCLUSION

Preoperative NLR can be a crucial marker in identifying complicated paediatric appendicitis and predicting postoperative complications, aiding resource allocation and surgical prioritization. Our findings suggest that paediatric surgeons should consider incorporating NLR in decision-making, especially in cases where history and physical examination are inconclusive due to communication challenges.

ETHICS APPROVAL: The ERC gave ethical review approval.

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin.

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