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The Relationship between Neutrophil-Lymphocyte Ratio to Intestinal Viability in Invagination Patients at Dr. M. Djamil General Hospital, Padang, Indonesia

Romi Ranuta^{1*}, Jon Efendi¹, Budi Pratama Arnofya¹, Yevri Zulfiqar¹, Benni Raymond¹, Hendra Maska¹

¹Department of Surgery, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

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*Corresponding author:

Romi Ranuta

E-mail address:

romi.ranuta@gmail.com

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ABSTRACT

Background: Invagination is an acute condition in the pediatric abdomen that results in obstruction and constriction of blood vessels (strangulation) in the proximal intestinal mesentery trapped in the distal intestine, allowing necrosis of surrounding tissue. Intestinal necrosis and perforation in children are causes of abdominal emergencies that require immediate surgery. In supporting examinations, neutrophil, lymphocyte, and biomarker combination ratios have been used for early detection of systemic inflammatory markers. The threshold value of several biomarkers should be investigated to assess the occurrence of strangulation in the pre-operative period in invaginated patients. This study aimed to determine the relationship between neutrophil-lymphocyte ratio and intestinal viability in pediatric patients with invagination. **Methods:** This study used retrospective analytic data collection from medical records of invagination patients at Dr. M. Djamil General Hospital Padang for the period January 1, 2020, to December 31, 2022. **Results:** The majority of subjects were male (53.8%) at the age of ≤ 1 year, with as many as 87.2% having a diagnosis of operative invagination (76.9%) and 56.4% having intestinal viability. The mean neutrophil, lymphocyte, and NLR values were 62.15 ± 17.68 , 19.03 ± 8.97 , and 3.74 ± 1.55 , respectively. The pathological NLR status was found to be 59%. The p-value for the association of diagnosis with intestinal viability was 0.002. The p-value for the relationship between NLR and intestinal viability was 0.001, and the r-calculated was -0.528. **Conclusion:** There is a significant relationship between NLR value and disease diagnosis on intestinal viability.

1. Introduction

Invagination is an acute condition in the abdomen of children that must be treated immediately because it has the potential to be dangerous. In addition to causing obstruction, invagination also results in the narrowing of blood vessels (strangulation) in the proximal intestinal mesentery trapped in the distal intestine, which allows necrosis of surrounding tissues. Necrosis and intestinal perforation in children are two of the causes of abdominal emergencies that require immediate surgery.¹

In addition to clinical symptoms and hematological examination, radiology also has an important role in diagnosing invagination. Ultrasound is the first-line

examination to confirm the diagnosis. Ultrasound examination shows a picture of sausages with heterogeneous echogenic masses with layered layers that give a sandwich-like image (pseudo kidney sign) in the longitudinal location, and the target sign is in a transverse location. Radiographic photography with barium enema administration is performed if the patient is in stable condition and is used for diagnostic or therapeutic purposes. CT scans of the abdomen have revealed proximal intestinal invagination (ileo-ileal) with a cocoonlike appearance.²

Histologically, it concerns a complex series of events, including dilatation of arterioles, capillaries, and venules, accompanied by increased permeability

and blood flow, the exudation of fluids, including plasma proteins, and the migration of leukocytes to foci of inflammation.³ Leukocyte count, platelet count, and neutrophil ratio are often used as hematologic inflammatory markers, especially the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. The neutrophil-lymphocyte ratio and platelet-lymphocyte ratio are further abbreviated as NLR and PLR, respectively. Increased neutrophils and lymphopenia during general inflammation. Therefore, NLR reflects the occurrence of an inflammation.³

Several biomarkers of systemic inflammatory markers, such as neutrophils, CRP, albumin, platelets, lymphocytes, and biomarker combination ratios, have been used for the early detection of various conditions such as pancreatitis, appendicitis, cancer, or ischemic mecentric. Especially for the combination of inflammatory factors such as NLR, PLR, and CAR (CRP-albumin ratio), it has been suggested that it be used in invagination patients to assess the occurrence of necrosis. The threshold values of some of these biomarkers should also be investigated to assess the occurrence of strangulation in the preoperative period in invaginated patients.⁴

Invagination can cause strangulation, which can lead to intestinal ischemia and necrosis due to blockage of blood flow. Surgery for invagination is essential to avoid ischemia and intestinal necrosis because a delayed response can lead to unnecessary bowel resection, sepsis, and even death.⁶ Until now, there has been no research on the relationship between NLR and intestinal viability in invagination patients, but there are several other studies that examine the relationship between NLR and intestinal viability in other gastrointestinal cases. With the similar pathophysiology of the case and the lack of resources and energy to determine the progression of invagination in children, researchers are interested in conducting research on the relationship between NLR and intestinal viability with invagination in children.

2. Methods

This study was conducted using retrospective analytical methods to assess the relationship between NLR values and intestinal viability in invagination patients at Dr. M. Djamil General Hospital Padang. This study is a consecutive sampling using medical record data of pediatric patients with invagination at Dr. M. Djamil General Hospital Padang for the period January 1, 2020, to December 31, 2022. The variable studied is the independent variable, namely the neutrophil-lymphocyte ratio, and the dependent variable is intestinal viability in invagination. Univariate data processing using the frequency distribution of sample characteristics and bivariate data processing using the Chi-square test with a p-value < 0.05. Data processing using the program SPSS Statistics 23.

3. Results

A study was conducted on the relationship of neutrophil-lymphocyte ratio (NLR) to Intestinal Viability in Invaginated patients at Dr. M. Djamil General Hospital Padang using a retrospective analytic design through processing complete medical record data of pediatric patients with invagination at Dr. M. Djamil General Hospital Padang for the period January 1, 2020 - December 31, 2022. In 39 research subjects with the following characteristics:

The majority of research subjects were men (53.8%), and the largest age group was ≤ 1 year, as much as 87.2%. The most diagnoses were obtained by patients with operative invagination, at 76.9%. Intestinal viability was classified as viable by 56.4% of study respondents. Neutrophil values were obtained on average at 62.15 ± 17.68 , average lymphocyte values were 19.03 ± 8.97 , and the average NLR was 3.74 ± 1.55 . Pathological NLR status was obtained at 59%.

From the table below, it was found that 75% of patients with invagination experienced impaired intestinal viability. A p-value of $0.002 < 0.05$ is obtained, which means that there is a significant relationship between disease diagnosis and intestinal viability.

Table 1. Characteristics of respondents.

Characteristics	Value
Age (year) f(%)	
≤ 1 year	34(87,2)
> 1 year	5(12,8)
Gender f(%)	
Male	21(53,8)
Female	18 (46,2)
Diagnosis f(%)	
Conservative invagination	9(23,1)
Operative invagination	30(76,9)
Intestinal viability f(%)	
Viable	22(56,4)
Nonviable	17(43,6)

Table 2. NLR parameters of invagination patients.

Parameters	Value
Laboratory mean±SD	
Neutrophil	62,15±17,68
Lymphocyte	19,03±8,97
Neutrophil to lymphocyte ratio	3,74±1,55
NLR status f(%)	
Physiological	16(41)
Pathological	23(59)

Table 3. Relationship of intestinal viability in children with invagination disease.

		Intestinal viability (%)		p-value	Result
		Nonviable	Viable		
Diagnosis (%)	Conservative invagination	1(11,1)	8(88,9)	0.002	Significant
	Operative invagination	21(70)	9(30)		
	Total	22(56,4)	17(43,6)		

Table 4. Relationship of NLR value to intestinal viability in invagination.

		Intestinal viability (%)		R-calculate	p-value	Result
		Nonviable	Viable			
NLR status (%)	Physiological	4(25)	12(75)	-0.528	0.001	Significant
	Pathological	18(78,3)	5(21,7)			
	Total	22 (56,4)	17(43,6)			

From the table above, it is found that the p-value is 0.001 and the calculated r is -0.528. The r value of the table in the 39 samples was -0.316. So that we get $r_{\text{calculate}} > r_{\text{table}}$, which is $-0.528 > -0.316$ and $p\text{-value } 0.001 < 0.05$. The results of this study mean that there is a significant negative relationship between NLR values and intestinal viability in child invagination. This means that if the NLR value increases, intestinal viability decreases.

4. Discussion

Invagination is a digestive condition that describes the involution of the proximal part of the intestine into

a more distal part, which often leads to intestinal obstruction. In a study by Lin (2019), found that there are more male patients than female patients, with the male:female ratio being 4:1 and the majority of patients aged 2 to 5 years (47.7%), and these patients are more likely to experience pathologic lead points (PLPs) than those aged <2 years.⁵ In line with the results of research by Zhao (2019), the majority of invaginations occur in boys (63.9%) with an age of < 2 years (56.6%). Most invaginations occur in children younger than 1 year old, and almost all invaginations that occur in children older than 5 years are the result of PLP.⁶

In research related to the decision on the management of small bowel obstruction (SBO) cases in terms of the time of symptom presentation conducted by Liu et al. (2023), it was found that the etiology of SBO occurred mostly by congenital or adhesion with a total of 44 cases (58.67%), while intussusception was the second most common cause with 15 cases (20%).⁷ According to Nail 2016, if CT results and findings lead to self-healing intussusception, conservative management is performed according to a serial abdominal examination, intestinal restoration, intravenous fluids, and appropriate laboratory as needed, along with follow-up imaging studies to assess the etiology and status of the intussusception. In recurrent cases, further GI evaluation is required. With a conservative approach and no evidence of other adjoining pathologies, emergency laparotomy can be avoided. In unclear cases, diagnostic laparoscopy can aid in decision-making, surgical planning, and treatment of patients.⁸

The NLR value reflects the number of counting neutrophils and lymphocytes in the blood that can increase the incidence of sepsis development and multi-organ failure.⁹ The same study by Liu et al. (2023) showed variations in NLR values with an increasing trend, with values of 0.92 in the control group, 1.07 in the infected group, and 1.65 in the sepsis group, indicating a link between sepsis incidence and NLR values.⁷

Proinflammatory and inflammatory processes can increase the risk of an uncontrolled innate immune system, cause tissue damage, and cause septic shock and organ failure due to the aggressive activation of defense mechanisms. Instead, lymphocytes are thought to play a key role in immune suppression through healing and repair processes involving inflammation and damaged tissue. NLR values reflect the balance between the immune system and the immunosuppression system in patients with SIRS. Thus, an elevated NLR indicates an imbalance in the immune system, and these findings have been reported as predictors of mortality in septic patients.¹⁰

Judging from other aspects, NLR has great advantages due to its simplicity, economic efficiency, and easy availability and can be easily calculated in any ER. NLR values do not require additional laboratory evaluation or further cost, unlike other biomarkers. In addition, the study suggests that NLR may be useful for emergency physicians, as it can help predict hospital deaths among SBO patients who require aggressive care, such as fluid resuscitation, and who are considered for surgical intervention.¹⁰

Based on Ghritlaharey's (2021) retrospective study on pediatric invagination surgery <12 years in India for the period 2000-2021, it was found that ileocolic/colo-colic is the most common type of anatomy and was documented in n = 183 (86.32%) children, followed by ileo-ileal, n = 27 (12.73%), jejunojejunal, n = 1 (0.47%), and postoperative type, n = 1 (0.47%).¹¹ For pediatric patients who present with suspected SBO, an early surgical evaluation should be performed.¹² Conservative treatment, including fasting, nasogastric suction, and fluid therapy, is the first choice in adult patients and has a success rate of 16%-63%.¹³ Currently, the main modality for the treatment of intussusception in children is hydrostatic reduction or nonoperative pneumatics under radiological or ultrasound guidance, which is mostly practiced in developed countries with a success rate of over 95% and is directly related to the initial presentation and diagnosis of intussusception. These modalities were chosen because they have the added advantage of shorter hospitalization times¹ as well as lower morbidity rates.¹¹

Batebo et al.¹³ showed that children with SBO who underwent surgical intervention within 24 hours of symptom onset had fewer incurable incidences of intestinal ischemia and postoperative complications. Children with SBO who present with lethargy, persistent abdominal pain, abdominal distention, and signs of peritoneal irritation, which strongly point to bowel strangulation, usually require emergency surgery. If the rate of intestinal resection is significantly higher in patients with a duration of symptoms of ≥48 hours. Early surgical intervention for

pediatric patients with SBO can avoid unnecessary bowel resection as well as reduce perioperative morbidity and mortality.⁷

Research by Yao et al. (2015) states that loss of intestinal viability in the group of invagination cases is significantly associated with the length of the history of the disease ($P = 0.000$). In addition, the risk of loss of intestinal viability is higher in women (31%) than men (20.8%) ($P = 0.049$). The rate of loss of intestinal viability was also significantly higher in cases of ileo-ileal invagination compared to other types ($P = 0.033$). However, there was no difference between the other groups.¹⁴

Surgical therapy available for the treatment of intussusception in children can cause complications in the form of peritoneal abscess, anastomosis leakage, peritonitis, wound dehiscence, postoperative adhesions, and incisional hernias. Some of these require re-exploration to manage their complications.¹⁵ In Ghritlaharey's study, nine children (4.24%) also required re-exploration for their complication management. Postoperative complications that require re-exploration are anastomosis leakage, abdominal perforation, wound dehiscence, and stoma necrosis.¹¹

In developed countries, the mortality rate for the treatment of intussusception in infants and children is less than 1%, and this is associated with early diagnosis, and the use of radiological reduction of intussusception. In addition, mortality rates related to surgical treatment for childhood intussusception are also reported to be less than 1% in developed countries.^{11,16}

Contrary to previous data, in developing countries, mortality associated with the management of intussusception in infants and children is much higher, at 7 to 10%. It is directly associated with delayed diagnosis, delay in referral and diagnosis, the presence of intestinal gangrene, required intestinal resection, and therapeutic surgery.¹¹

Small bowel obstruction (SBO) is a relatively common disease entity in the emergency department (ER), requiring approaches ranging from conservative

treatment to emergency surgery. In the ER, proper SBO management has become a common clinical challenge because it is difficult to perform on patients who show vague symptoms in the absence of signs of strangulation or peritonitis, requiring mandatory emergency surgery. After conservative treatment within a few days fails, surgical intervention is required. However, there are certain risks of delaying the diagnosis of strangulation, and this can lead to poor outcomes. A physical examination alone is not enough for decision making.¹⁰

Most invaginations can be treated by nonoperative reduction via barium enema with fluoroscopy guidance and pneumatic reduction, and emergency surgery should still be performed in cases where nonoperative reduction fails.¹⁷ In terms of surgical planning and patient management, it is critical to detect potential complications early, as delays can result in impaired intestinal circulation, which can lead to life-threatening secondary intestinal necrosis, perforation, or peritonitis, resulting in bowel resection and death.¹⁸ Further tests have been applied in determining the prognosis of SBO, such as the use of contrast agents and abdominal CT scans, to overcome the lack of insufficient physical examination in the determination of operative measures.¹⁰

The ratio of neutrophils to lymphocytes (NLR) has been used as a predictor of prognosis and a marker of disease severity for various diseases, such as infections, thrombotic events, and various types of cancer, since it was first reported in 2001.¹⁹ In addition, NLR has been reported as a valuable diagnostic tool in the decision-making process for surgical procedures in cases requiring immediate intervention, such as acute appendicitis, acute cholecystitis, and incarcerated hernia.²⁰

The study by Yun and Lee (2020) is the first study related to the relationship between NLR and the prognosis of SBO patients. The results revealed NLR as an independent predictor, where there is a positive association between high NLR and poor SBO prognosis, as evidenced by hospital deaths.¹⁰ NLR values do not yet demonstrate predictive power for

operative decision, but based on other reports, high NLR levels measured in the ER are independently associated with hospital mortality, multi-organ failure, and sepsis progression.^{9,21} Research by Yoon and Lee (2021) revealed a cutoff value for poor SBO prognosis, i.e. NLR values greater than 10.6 upon initial patient arrival in the ER, where emergency physicians should keep in mind the possibility of poor SBO prognosis and should consider more aggressive and careful resuscitation and appropriate management.¹⁰

Idiopathic ileocolic invagination is the most common form in children and is usually treated by nonoperative reduction through pneumatic and/or hydrostatic enemas. In the adult population, invagination is rare and more common in the small intestine than the large intestine. It is associated with Pathologic Lead Points in most cases of symptoms that appear as intestinal obstruction. When Pathologic Lead Points are present in an adult small intestine invagination, they are usually benign, although when malignant, they are most often caused by a metastatic disease that has spread, such as melanoma.¹

NLR has been recognized as a reliable marker for the diagnosis of bacteremia and sepsis.²² Value of preoperative NLR as an independent predictor for postoperative complications, as well as peri-procedural and post-procedural mortality, regardless of the type of surgery (heart or abdominal surgery).²² NLR is an inexpensive, simple, responsive, and easily available stress and inflammation parameter with high sensitivity and low specificity to be used routinely in emergency departments, ICUs, and acute medicine, including surgery, orthopedics, traumatology, cardiology, neurology, psychiatry, and even oncology.²³

Intestinal obstruction can occur due to malignant causes as well as benign occurrences. Benign causes of intestinal obstruction include inguinal, femoral, umbilical, and incisional hernias, adhesions, invaginations, internal herniations (postoperative or congenital), volvulus of the small and large intestines, and idiopathic colon pseudo-obstruction. If surgical intervention is delayed, and it is likely that ischemia

may develop within a few hours.²⁴ Similar conditions can also arise as a result of delayed surgical treatment associated with intestinal obstruction from other non-malignant causes such as invagination, intestinal volvulus, and idiopathic intestinal pseudo-obstruction. The physiological response of the immune system to various stress factors results in an increase in the number of neutrophils and a decrease in the number of lymphocytes.²⁵

In secondary intestinal obstruction due to benign causes, there can sometimes be delayed cases because there are no clear restrictions on when to perform surgery. This leads to bowel resection, increased morbidity and mortality, and a longer duration of hospital stay due to ischemia and perforation. Many studies have shown that NLR is a very important parameter in predicting the severity and progression of pathology currents across various malignancies, chronic diseases, inflammation, and ischemic conditions.²⁶ In addition, inflammation and immunity play important roles in many chronic diseases.²⁷ NLR can predict mortality in the general population and thus the overall impact of inflammation and immunity on health.²⁵

Research by Tasci 2022 found that hospitalized patients with high NLR values due to benign intestinal obstruction had a significantly increased risk of ischemia, need for resection, postoperative complications, and death during surgery ($p < 0.05$). This study shows that NLR has a very important role in predicting the course of disease and surgical indications in benign intestinal obstruction.²⁶ A meta-analysis by Huang 2020.⁵⁷ showed that a higher NLR was associated with a lower prognosis in patients with sepsis (mean HR 1.75) and higher NLR values in non-survivors than sepsis survivors (mean HR 1.18).²² Another study by Carlos 2022, of 511 intussusception patients, found high NLR values implying high levels of intestinal inflammation and may anticipate the need for surgical treatment of Ileo-Colic Intussusception (ICI) in children, with an NLR cut-off point greater than 4.52 (sensitivity: 73.2%; specificity: 94.5%).²⁸ Based on the results of this study, NLR values can be used

as predictors that can assist health workers in providing informed consent and disease prognosis to patients and families.

5. Conclusion

The majority of research subjects were men (53.8%) and the largest age group was ≤ 1 year, as much as 87.2%. The most diagnoses were obtained by patients with operative invagination, at 76.9%. Intestinal viability was classified as viable. The average neutrophil, lymphocyte, and NLR values were 62.15 ± 17.68 ; 19.03 ± 8.97 ; and 3.74 ± 1.55 . The results showed a pathological NLR value of 59%. There was a significant association between diagnosis and intestinal viability (p-value $0.002 < 0.05$). There was a significant relationship between neutrophil lymphocyte ratio (NLR) and intestinal viability (p-value $0.001 < 0.05$).

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