Neutrophil-Lymphocyte Ratio Superior to Total Leukocyte and Neutrophil in Diagnosing Acute Appendicitis Using Alvarado Score

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Abstract:- Background: The diagnosis of acute appendicitis must be performed quickly and accurately to reduce the risk of negative appendectomy without increasing the risk of perforation. Objective: To analyze whether Neutrophil-Lymphocyte Ratio (NL-R) in the modified Alvarado score is more accurate in diagnosing acute appendicitis in comparison with total leukocyte and neutrophil. Method: This was a cross-sectional study and the data were collected from Telogorejo Hospital Semarang (Indonesia) from November 2018 until October 2019. The best cut-off point of NL-R for predicting acute appendicitis was provided through receiver operating characteristic (ROC) curve. NL-R was used to replace total leukocyte and neutrophil to form a modified Alvarado score. Area Under Curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the original Alvarado Score and modified Alvarado score were measured. Results: Sensitivity, specificity, positive predictive value, negative predictive value of the original Alvarado score are 100%, 84.6%, 91.3%, and 100% respectively with cut-off point total score of >4.5. Sensitivity, specificity, positive predictive value, negative predictive value of modified Alvarado score were 100%, 100%, 100%, and 100% respectively with cut-off point total score of >5.5. AUC modified Alvarado Score was 1.000 and AUC original Alvarado Score was 0.985. Conclusion: Modified Alvarado score diagnoses acute appendicitis more accurately than the original Alvarado Score.

Keywords:- Acute Appendicitis, Leukocyte, Neutrophil, NL-R, Original Alvarado Score, Modified Alvarado Score.

I.   INTRODUCTION

Acute appendicitis is the most frequent emergency case in emergency room.[1-6] The diagnosis of appendicitis is based on clinical history and physical examination.[1-7] The diagnosis of acute appendicitis is sometimes difficult especially during early stages because classical signs are present in only 50% cases. The diagnosis of acute appendicitis should be early and accurate because delay in diagnosis will increase perforation risk, and In contrast, incorrect diagnosis increases negative appendectomy. The risk of perforated appendicitis increases 5% every 12 hours period, 36 hours after onset of appendicitis symptoms.[1,2,8,9] The incidence of perforated appendicitis is 15-45% and the incidence of negative appendectomy 15-40%.[2,9] Perforated appendicitis rate of <20% and <15% rate of negative appendectomy are considered acceptable.[1-7,9-11]

Alvarado score is the most commonly used score all over the world[12] and a safe, non invasive, simple, easy, fast, and reliable diagnostic method of acute appendicitis.[10,11,13-15] The accuracy of Alvarado score varies, between countries 57%-90%.[12,16-19] C-Reactive Protein (CRP), an acute phase protein that is synthesized by liver, will increase in blood 12 hours after the onset of infection, and increase in parallel with the degree of infection and tissue damage. CRP peak is reached in 24-48 hours. CRP is usually used to diagnose perforated appendicitis.[2,11,12,17,20,21]

Neutrophils, the most important cells in infection, will increase 5 hours after the onset of infection. During the infection process, the increase of neutrophil count is followed by a relative decrease in lymphocyte count 6 hours after the onset of infection.[22,23] Neutrophil-Lymphocyte Ratio (NL-R) is the balanced ratio of neutrophils and lymphocytes. The increase in neutrophils correlates with the infection severity and stress condition.[3,4,21,24] NL-R is more specific and accurate than total leukocyte count.[3-5,25,26]

Ultrasonography (USG) helps in diagnosing acute appendicitis but the accuracy of USG in diagnosing acute appendicitis is 71-97%.[1,7,9,12] CT scan is the best diagnostic method for acute appendicitis, with an accuracy of 93-98% (with contrast) and 87-90% (without contrast), USG and CT scan are not always available in every health facility center, especially in the peripheral area because of their expensive costs.[6,9,27] Until this time, there is no symptom, sign, and diagnostic test that can accurately diagnose acute appendicitis and therefore the studies to find the more accurate way still continue.[1,9] In this study we used modified Alvarado score by replacing neutrophil and leukocyte count with NL-R. We hope that this study will produce a score to diagnose acute appendicitis as a simple, inexpensive, accurate, and widely available method in health facilities.

II. METHOD

This study was a cross-sectional study. Data were collected from Telogorejo Hospital, Semarang, Indonesia from November 2018 until October 2019. The data collected from medical records were 34 patients consisted of patients with complaints of right lower quadrant pain, have undergone appendectomy and the specimens were examined microscopically. The diagnosis of acute appendicitis was made based on pathologic result as a gold standard. The criteria of acute appendicitis were neutrophil infiltration in submucosa (simple appendicitis), mucosal ulceration and neutrophil infiltration in serosa (suppurative appendicitis), necrosis appendix wall, trombosed vein, neutrophil infiltration into serosa (gangrenous appendicitis), perforation until periappendicular area (perforated appendicitis) and acute exacerbation of chronic appendicitis considered as acute appendicitis in the analysis. The criteria of chronic appendicitis were lymphocyte in muscular layer and lumen fibrotic. Specimens of appendix that did not fulfill the above criteria were diagnosed as chronic appendicitis. The age, sex, the presence of epigastric or periumbilical pain that migrate to right ileac fossa (RIF), nausea or vomitus, tenderness and rebound tenderness of RIF, body temperature, and laboratory results of total leukocyte, percentage of neutrophil and lymphocyte, were all collected from patients' medical records. NL-R was provided by dividing percentage of neutrophil to percentage of lymphocyte.

The best cut-off point of NL-R to diagnose of acute appendicitis was provided through ROC Curve. Above the best cut-off point was considered positive and scored 3, because will be used to replace total leukocyte and percentage of neutrophil. Area under curve, sensitivity, specificity, positive predictive value and negative predictive value of original Alvarado Score and modified Alvarado score were measured.

III. RESULTS

From this study we collected 34 patients, 21 patients with acute appendicitis with mean age of 39 years and 13 patients with chronic appendicitis with mean age of 29.7 years. Among symptoms reported, abdominal pain that migrates to the RIF is found in 47.6% cases of acute appendicitis and 7.7% cases of chronic appendicitis. Anorexia is reported in 71.4% cases of acute appendicitis and 53.8% cases of chronic appendicitis. Nausea/vomiting is reported in 42.9% cases of acute appendicitis and 30.8% cases of chronic appendicitis.

Among signs documented, tenderness in Right Iliac Fossa (RIF) was present in 100% cases of acute appendicitis and 100% cases of chronic appendicitis. Fever (temperature > 37.3°C) is present in 66.7% cases of acute appendicitis and 0% case of chronic appendicitis. Among laboratory results, leukocytosis (>10.000) is found in 52.4% acute appendicitis cases and chronic appendicitis cases 0%. Neutrophilia (>75%) is found in acute appendicitis 66.7% and chronic appendicitis cases 0%, while lymphocytopenia (<20%) is

found in acute appendicitis 71.5% and chronic appendicitis 0%. Total Alvarado score >5 were found in acute appendicitis 81% and chronic appendicitis 0%.

Variables	Appendicitis		
	Acute n=21 (61.8%)	Chronic n=13 (38.2%)	P Value
Age	39.0±16.4	29.7±9.4	0.072
Sex			1.000
Female	15 (71.4)	10 (76.9)	
Male	6 (28.6)	3 (23.1)	
Abdominal pain that migrates to the RIF			0.024
Positive	10 (47.6)	1 (7.7)	
Negative	11 (52.4)	12 (92.3)	
Anorexia			0.462
Positive	15 (71.4)	7 (53.8)	
Negative	6 (28.6)	6 (46.2)	
Nausea or vomiting			0.718
Positive	9 (42.9)	4 (30.8)	
Negative	12 (57.1)	9 (69.2)	
Tenderness in RIF			
Positive	21 (100.0)	13(100.0)	
Negative			
Rebound tenderness			0.727
Positive	13 (61.9)	9 (69.2)	
Negative	8 (38.1)	4 (30.8)	
Fever			<0.0001
> 37.3	14 (66.7)	0 (0.0)	
< 37.3	7 (33.3)	13(100.0)	
Leukocytosis			0.002
>10000	11 (52.4)	0 (0.0)	
<10000	10 (47.6)	13(100.0)	
Neutrophilia			<0.0001
>75%	14 (66.7)	0 (0,0)	
<75%	7 (33.3)	13(100.0)	
Total Alvarado Score			<0.0001
>5	17 (81.0)	0 (0.0)	
<5	4 (19.0)	13(100.0)	
Lymphocyte			<0.0001
<20	15(71.5)	0(0.00)	
>20	6 (28.5)	13(100.0)	
NL-R			<.0.0001
>2.925	21(100.0)	0(0.00)	
<2.925	0(0.0)	13(100.0)	

Table 1:- Characteristic of the patients

A. Data Analysis

➤ *Total Alvarado score, neutrophil, lymphocyte, leukocyte counts, and NL-R.*

Result from an analysis by ROC (*Receiver Operating Characteristic*), with cut-off point, sensitivity, specificity.
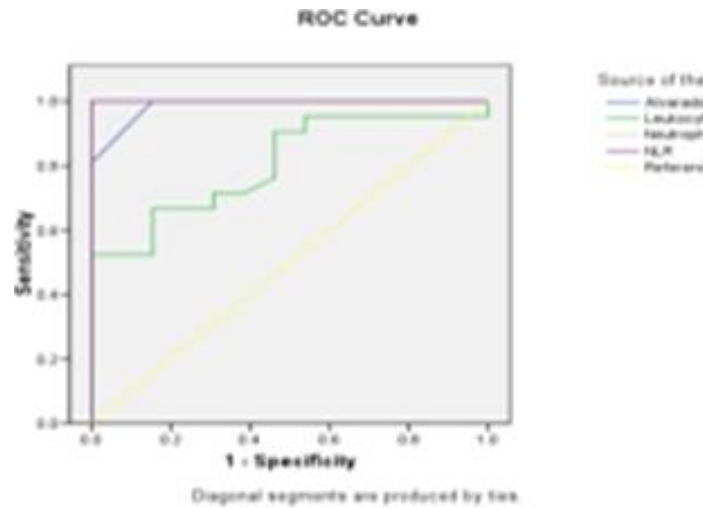
Fig 1:- ROC curve for total Alvarado, leukocyte, neutrophil, lymphocyte counts and NL-R. AUC total Alvarado: 0.985, AUC leukocyte t: 0.804, AUC neutrophil: 1.000, AUC lymphocyte: 1.000 AUC NL-R 1.000)

	AUC	CI 95%		Sensitivity	Specificity	PPV	NPV	Cut-off point	P Value
		Lower border	Upper border						
Total Alvarado	0.985	0.956	1.000	100%	84.6%	91.3	100	4.5	0.000
Leukocyte	0.804	0.657	0.951	66.7%	84.6 %	87.5	61.1	9.75	0.003
Neutrophil	1.000	1.000	1.000	100%	100%	100	100	69	0.000
Lymphocyte	1.000	1.000	1.000	100%	100%	100	100	23	0.000
NL-R	1.000	1.000	1.000	100%	100%	100	100	2.925	0.000

Table 2:- Summary of diagnostic value for leukocyte, neutrophil, lymphocyte count, total Alvarado score and NL-R

B. Based on ROC analysis result

Leukocyte p=0.003, neutrophil p=0.000, NL-R p= 0.00, which means NL-R, leukocyte, NL-R have significant prediction in diagnosing appendicitis. We uses chi square test to analyze which variables have a strong predisection with appendicitis diagnosis. The chi square test results for leukocyte is 8.476, neutrophil 34.0 and NL-R 34.0. In conclusion, NL-R can be used to substitute to leukocyte and neutrophil count in diagnosing appendicitis.

➢ *Data analysis of modified Alvarado score with variable NL-R*

Based on data analysis, NL-R can replaced leukocyte and neutrophil in diagnosing acute appendicitis. We modified the Alvarado score (Table 3) with 8 variables (3 symptoms, 3 signs, 2 laboratory results: leukocyte and neutrophil with total score 10) into modified Alvarado score 2 (Table 4) with 7 variables (3 symptoms, 3 signs dan 1 laboratory result: NL-R, with total score 10).

		Modified Alvarado score
Symptoms	Migratory RIF pain	1
	Nausea/vomiting	1
	Anorexia	1
Signs	Right iliaca fossa tenderness	2
	Elevation of temperature	1
	Rebound tenderness RIF	1
Laboratory finding	Leukocytosis	2
	Neutrophilic shift to the left (>75%)	1
		Total score 10

Table 3:- Original Alvarado Score

		Modified Alvarado score
Symptoms	Migratory RIF pain	1
	Nausea/vomiting	1
	Anorexia	1
Signs	Right iliaca fossa tenderness	2
	Elevation of temperature	1
	Rebound tenderness RIF	1
Laboratory finding	NL-R >2.925	3
		Total score 10

Table 4:- Modified Alvarado score

	AUC			Sensitivity	Specificity	PPV	NPV	Cut off point	P Value
		Lower border	Upper border						
Total modified Alvarado	1.00	1.00	1.00	100%	100%	100	100	5.5	0.000
Total original Alvarado	0.985	0.956	1.00	100%	84.6%	91.3	100	4.5	0.000

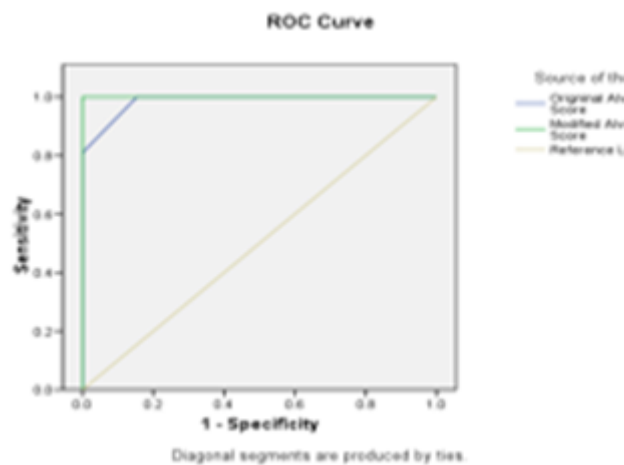Table 5:- Diagnostic value of total Alvarado score and modified Alvarado score

Fig 2:- ROC curve for original Alvarado Score dan modified Alvarado score (AUC Modified Alvarado: 1.000, AUC Original Alvarado: 0.985)

IV. DISCUSSION

We found 34 patients from November 2018 until October 2019. Abdominal pain that migrates to the RIF (47%) was more frequent and was followed by anorexia. This is different from other literature: nausea/vomiting is more frequent (64%), because symptoms are unique, individual and vary according to patient's response to the inflammation. Nausea /vomiting because of distention of appendix lumen and stimulation of vagal nerve.[1,18,19,28] Tenderness in RIF, was he most frequent sign 100% in this study and equal with literature. Tenderness in RIF is the classic sign of acute appendicitis. Because base of appendix is constant with caecum, and pain because the inflamed appendix irritate the peritoneum.[1,2,18,19,26]

10 patients (47%) have normal leukocyte count with neutrophil >70-75% for 5 patients (23%) and neutrophil >75% for 5 patients (23%). Acute appendicitis with normal leukocyte were 10 patients (47%), higher than other literature in which normal leukocyte count in acute appendicitis is 20-25%. This study found neutrophil >75% in leukocytosis: 8 patients (72.2%) lower than literature: 75-80% patients with leukocytosis had neutrophil >75%. Neutrophil is the biggest component in leukocyte and will increase in 5 hours after the onset of the infection and leukocyte count was normal in 75-80% cases after 24 hours of infection.[1,14,29,30] Cut-off point for NL-R in this study was 2.925, which is equal to other studies. Based on other literature normal NL-R varies between 0.78-3.53. The variations of NL-R depends on age, sex, genetic, physiology stress, diet, environment and antibiotic use.[1,3,4,5,14,31]

Results of diagnostic test of modified Alvarado score with cut-off point 5,5: sensitivity 100% specificity 100% and AUC 1.00, which means modified Alvarado score is more accurate than original Alvarado score. NL-R value is higher compared with leukocyte and equal to neutrophil in diagnosing acute appendicitis, based on Alvarado score. This finding is similar with other literature because NL-R consists of two biggest components of leukocyte that are neutrophil (hallmark of acute inflammation) and lymphocyte (important indicator for inflammation). NL-R integrates two biggest component of immune system in one marker. A large number of neutrophils are needed to destroy the bacteria.[3,8,9,13,16,29] The increase in neutrophils correlates with the infection severity and stress condition and the increase of neutrophil count is followed by a relative decrease in lymphocyte count, 6 hours after the onset of infection.[3,4,21,22-25]Neutrophil shift to the left begins in 12-24 hours because of stimulus in healthy condition or pathological condition but sudden change and significant only happen in bacterial infection, which makes it an accurate indicator to reflect the mild to serious condition of the bacterial infection.[3,4,23,26,32]

V. CONCLUSION

From this study we found that for original Alvarado score gave results of variable neutrophil with cut-off point >69%, leukocyte cut-off point >9.75 and Alvarado score cut-off point >4.5. In this study we discovered NL-R with cut-off point > 2.925 for diagnosing acute appendicitis and modified Alvarado score of variable NL-R with cut-off point >2.925 and total modified Alvarado score >5.5 (specificity 100%, sensitivity 100%, PPV 100%, NPV 100%). We found that modified Alvarado score is useful to diagnose acute appendicitis more accurately than original Alvarado score. The limitation of this study is the small sample size due to time constraint.

VI. RECOMMENDATION

Every case suspected for acute appendicitis should have differential blood count to measure the neutrophil, lymphocyte and NL-R. We suggest a continuing study with greater number of sample to calculate a cut-off point for NL-R and total modified Alvarado score more accurately to be an ideal test for diagnosing acute appendicitis.

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