ARTIKEL PENELITIAN

Accuracy of D-Dimer Levels and C-reactive Protein in Predicting Perforation of Acute Appendicitis

Gema Putra Lesmana[1], Reno Rudiman[2], Rani Septrina[2]

[1] *Surgery Department,* Hasan Sadikin Hospital, *Universitas Padjadjaran, Bandung*

[2] *Division Digestive Surgery, Surgery Department,* Hasan Sadikin Hospital*, Universitas Padjadjaran, Bandung*

Abstract

Introduction: D-Dimer as the primary product of fibrin degradation, was found to be increased in appendicitis patients. CRP still gives different results in predicting perforated appendicitis. The purpose of this study is to find out the accuracy of D-Dimer and CRP in predicting appendicitis perforation at the Central General Hospital Dr. Hasan Sadikin Bandung 2019.

Method: This study used prospective observational design with cross-sectional approach. The subject were taken from the Emergency Department (ED) patient between September 2018-September 2019 who met the inclusion criteria. Preoperative D-Dimer and CRP serum were measured and the results of the surgery were noted. Chi-Square test was conducted and the data were analyzed using SPSS Version 22.0 for windows at a 95% confidence level. The value is significant if $p < 0.05$.

Results: The sample included in this study were 41 patients, with 24 perforated appendicitis patients. The average age of patients was 34.8 ± 13.8. The majority of patients were male, 24 patients (58.5%). Area for ROC curve for D-Dimer is 0.929, with a cut-off point of 0.51 mg / l for sensitivity perforation appendicitis 95.8%, specificity 76.5%, positive predictive value (PPV) 85.2%, negative predictive value (NPV) 92.9% and accuracy 87.8%. For CRP with a cut-off point at 18.84 for sensitivity perforation appendicitis 58.3%, specificity 94.1%, positive predictive value (PPV) 93.3%, negative predictive value (NPV) 61.5% with an accuracy of 73.2%.

Conclusion: D-dimer and CRP level can be used in predicting perforation of appendicitis.

Keywords: D-Dimer, CRP, acute appendicitis, perforated appendicitis

ARTIKEL PENELITIAN

Correspondence:

Gema Putra Lesmana

Surgery Department, Universitas Padjadjaran, Bandung

Jalan Pasteur no. 38, Pasteur, Sukajadi, Bandung

Email : gemaputra240907@gmail.com

Introduction

Appendectomy has long been recommended to be performed in acute appendicitis cases because of the highly percentage of perforation. Jaffe and Berger (2010), put the overall rate of appendicitis perforation at 25.8%. Children aged less than 5 years old and adults over 65 years have the highest number of cases (45% and 51%, respectively). One common factor of perforated appendicitis is delayed time in seeking surgical treatment. There is no accurate examination that can show the timing of perforation in acute appendicitis.[1]

One study stated that the incidence of appendicitis perforation in adults ranges from 4-19%.[2] A good history taking and physical examination in appendicitis cases is believed to be as accurate as other laboratory examination modalities in establishing the diagnosis. Perforated appendicitis cannot be clearly distinguished from non-perforated appendicitis based on history taking and physical examination findings at the hospital. Late diagnosis can increase morbidity and mortality due to the risk of appendicitis perforation.[3] In elderly patients it is often difficult to determine acute appendicitis or perforated appendicitis, even with CT scans. From a study conducted by Tau Hyung Kim et al., from a total of 119 patients suspected of acute appendicitis, 21 patients had perforation.[4]

Appendicitis perforation is commonly diagnose intraoperatively. False diagnosis of appendicitis perforation in old patient is quite high, reaching 50%.[5] Other literature also stated that misdiagnosis and and the incidence of perforation in appendicitis was still high (15.3%).[1]

Examination of leukocyte, CRP (C-Reactive Protein), and bilirubin level has previously been able to predict the severity of acute appendicitis, but has not been able to provide convincing results. In the study of Farooqui et al these biomarkers shown a low sensitivity, whereas in the study of Maru Kim et al. CRP has a high sensitivity to perforated appendicitis.[6-8] Some studies have also tried to establish a diagnosis with a scoring system such as the Alvarado score, PAS (Pediatric Appendicitis Score) and AIR (Appendicitis Inflammatory Response). All types of scoring systems have proven to be very useful in predicting acute appendicitis in patients with lower right abdominal pain, but were still unable to evaluate the risk of perforated appendicitis.[7,9]

D-Dimer is the degradation production of fibrin. The level is increased in the incidence of thrombosis or in situations of inflammation, trauma, infection, ischemia, and DIC. D-Dimer is found to be increased in the incidence of acute appendicitis in children, this is because appendicitis is irritating peritoneal parietal, ischemic, then fibrinolysis occurs. However, D-Dimer has a low sensitivity for acute appendicitis. Therefore, researchers want to examine the accuracy of D-Dimer levels in perforated appendicitis.

The purpose of this study is to find out the accuracy of D-Dimer and CRP in predicting appendicitis peforation at the Central General Hospital Dr. Hasan Sadikin Bandung 2019.

Methods

This research was a prospective observational study with a cross-sectional approach. The population of this study were all patients who came to the ED of Hasan Sadikin General Hospital for the period of September 1st 2018 - September 31st 2019 who met the inclusion criteria. Inclusion criteria: patients with clinical diagnosis of acute appendicitis without complications or perforation, 18 years of age or older, willing to undergo appendectomy surgery, sign an agreement for research involvement. The patient then be examined for D-Dimer and CRP levels. The patient then undergoing appendectomy and the findings of the surgery were appendicitis with or without perforation. Surgical findings were noted, data grouping and analysis were performed after the number of research subjects was met. Chi-square test, measurement of AUC value in the ROC curve was carried out in this study and data were analyzed using SPSS Version 24.0 at 95% confidence level with a p-value significant if $p < 0.05$. This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Padjadjaran University, Bandung with No: LB.02.01 / X.6.5 / 124/2019.

Result

The sample included in this study were 41 patients with acute appendicitis who met the inclusion criteria. Of the 41 acute appendicitis analyzed, 24 patients or 58.5% shown perforated appendicitis, while the rest were classified as non-perforated appendicitis, 17 patients or 41.5% of the sample **(Table 1)**.

The discrimination ability of the D-Dimer, as well as the cut-off point of the categorization of D-Dimer levels as a predictor of perforation in the case of

appendicitis were analyzed based on the results of the ROC (Receiver Operating Characteristic) analysis. (**Figure 1**) The discrimination ability of D-Dimer to predict the occurrence of perforation in patients with acute appendicitis, as indicated by the value of Area Under Curve (AUC), was equal to AUC = 0.929 or 92.9% (p = 0,000).

Based on the analysis of the ROC curve for D-dimers on the status of perforated appendicitis, the D-Dimer score cut-off value of 0.51, which classifies D-Dimer levels ≥ 0.51 (perforated appendicitis) and < 0.51 (without perforation). This cut-off value of 0.510 has a maximum J-Youdent statistical value, which is sensitivity - [1 - specificity] = 0.958 - 0.235 = 0.723 (has a sensitivity of 95.8% and specificity of 76.5%). The cut-off value with maximum J-Youdent is the cut-off value which has the optimal accuracy value from various cut-off alternatives obtained (Figure 1).

(**Figure 2**) Based on the results of the ROC curve analysis for CRP the CRP cut-off score of 18.84 was obtained, which classifies CRP levels into ≥18.84 (perforated appendicitis) and <18.84 (non-perforated appendicitis). This cut-off value of 18.84 has a maximum J-Youdent statistical value, which is sensitivity - [1 - specificity] = 0.583 - 0.059 = 0.525 (has a

sensitivity of 58.3% and specificity of 94.1%) (Figure 2).

Chi-Square test results prove the accuracy of D-Dimer in predicting the occurrence of perforation in appendicitis patients is 87.8% (p = 0,000). Its sensitivity and specificity are 95.8% and 76.5%. D-Dimer is a significant predictor in predicting perforation in appendicitis cases (**Table 2**).

(**Table 3**) Chi-Square test results prove the accuracy of CRP in predicting the occurrence of perforation in patients with acute appendicitis is 73.2% (p = 0.002); lower than D-Dimer. The sensitivity and specificity are 58.3% and 94.1%.

Discussion

Acute appendicitis is associated with a systemic inflammatory response that often causes activation of coagulation. In this study high levels of serum D-Dimer and CRP were associated as predictive markers for perforated appendicitis.

From our results, there were 41 patients diagnosed with appendicitis based on the clinical finding which consisted of 24 patients with perforated appendicitis (58.5%), while the rest were classified as non-perforated appendicitis, which was 17 patients (41.5%) .

The mean age of appendicitis patients was 34.8 ± 13.8 years with a median of 36 years and an age range between 18 - 74 years. Acute appendicitis patients classified as perforated appendicitis had an average age of 36.8 ± 14.7 years, while those classified as non-perforated appendicitis have an average age of 31.8 ± 12.3 years. This founding is similar with the literature which stated that the incidence of appendicitis was most prevalent in the second decade to the third decade.[1]

In the retrospective study of Mentes et al., no significant differences were found in the D-Dimer level between appendicitis and non appendicitis groups. In a study conducted by Cayrol et al., in pediatric patients, there was a significant difference in D-Dimer levels between acute appendicitis and perforated appendicitis with a cut-off point of 230 ng/dl. In their study, the level of D-Dimer in acute appendicitis was higher compared to other diseases that caused lower right abdominal pain.[10,11]

In our study, D-Dimer cut-off score of 0.51 was obtained which classifies D-Dimer levels ≥0.51 (perforated appendicitis) and <0.51 (non-perforated appendicitis). This result shows that perforated appendicitis patients have higher

serum D-Dimer levels than acute appendicitis. This is consistent with the hypothesis that appendicitis patients irritate the parietal peritoneum and cause ischemia in the appendix wall which makes fibrinolysis and increases D-Dimer level.[10]

Previous studies have shown that CRP has a sensitivity of 70% and a specificity of 65%. In the study of Cayrol et al., at the same cutt-of point the sensitivity was 38% and the specificity was 85%.[10] In our study a CRP cut-off score of 18.84 was obtained, which classifies CRP levels into the categories ≥18.84 (perforated appendicitis) and <18.84 (non-perforated appendicitis), with a sensitivity of 58.3% and specificity at 94.1%.

In our study, the P-value was p <0.05, so it can be concluded that there is a very significant relationship between the increase in serum D-Dimer and CRP with perforated appendicitis. From the results of the study also obtained high sensitivity and specificity from changes in serum D-Dimer levels, namely sensitivity of 95.8% and specificity of 76.5%. The high level of sensitivity and specificity of serum D-Dimer levels in predicting the occurrence of perforation shows that serum D-dimer levels can be used as a diagnostic tool for perforation in appendicitis patients. The CRP in our study had a sensitivity of 58.3%

ARTIKEL PENELITIAN

and specificity of 94.1%. Therefore D-Dimer accuracy (87.8%) in predicting the occurrence of perforation in appendicitis cases is better than CRP (73.2%).

Conclusion

Increased serum D-Dimer and CRP levels can be used to predict the occurrence of perforation in appendicitis patients. But D-Dimer is better at predicting perforated appendicitis than CRP.

References

1. Greg J, Berger D. the Appendix. Dalam: Brunicardi FC, editor. Schwartz's Principle of Surgery.Edisi 9: McGraw-Hill; 2010. hlm. 1073-89.

2. Sammalkorpi HE, Leppaniemi A, Mentula P. High admission C-reactive protein level and longer in-hospital delay to surgery are associated with increased risk of complicated appendicitis. Langenbeck's archives of surgery. 2015;400(2):221-8.

3. William H P, Douglas S S. Appendix. 12 ed. Michael J. Zinner SWA, editor. New York: Mc-Graw Hill; 2013. hlm 623-648.

4. Kim TH, Cho BS, Jung JH, Lee MS, Jang JH, Kim CN. Predictive Factors to Distinguish Between Patients With Noncomplicated Appendicitis and Those With Complicated Appendicitis. Annals of Coloproctology. 2015;31(5):192-7.

5. Franz M. Increased morbidity of appendicitis with advancing age. Am Surg. 1995;61(1):40-4.

6. Farooqui W, Pommergaard HC, Burcharth J, Eriksen JR. The diagnostic value of a panel of serological markers in acute appendicitis. Scandinavian Journal of Surgery. 2014;104(2):72-8.

7. Kim M, Kim SJ, Cho HJ. International normalized ratio and serum C-reactive protein are feasible markers to predict complicated appendicitis. World journal of emergency surgery : WJES. 2016;11:31.

8. Nazmi A, Victora CG. Socioeconomic and racial/ethnic differentials of C-reactive protein levels: a systematic review of population-based studies. BMC Public Health. 2007;7:212-.

9. Giordano S, Pääkkönen M, Salminen P, Grönroos JM. Elevated

ARTIKEL PENELITIAN

serum bilirubin in assessing the likelihood of perforation in acute appendicitis: A diagnostic meta-analysis. International Journal of Surgery. 2013;11(9):795-800.

10. Cayrol J, Miguez MC, Guerrero G, Tomatis C, Simal I, Marañón R. Diagnostic accuracy and prognostic utility of D Dimer in acute appendicitis in children. European Journal of Pediatrics. 2016;175(3):313-20.

11. Akyildiz HY, Sozuer E, Akcan A, Kucuk C, Artis T, Biri I*, et al.* The value of D-dimer test in the diagnosis of patients with nontraumatic acute abdomen. Ulusal travma ve acil cerrahi dergisi = Turkish journal of trauma & emergency surgery : TJTES. 2010;16(1):22-6.

Table 1. Characteristic of Patients

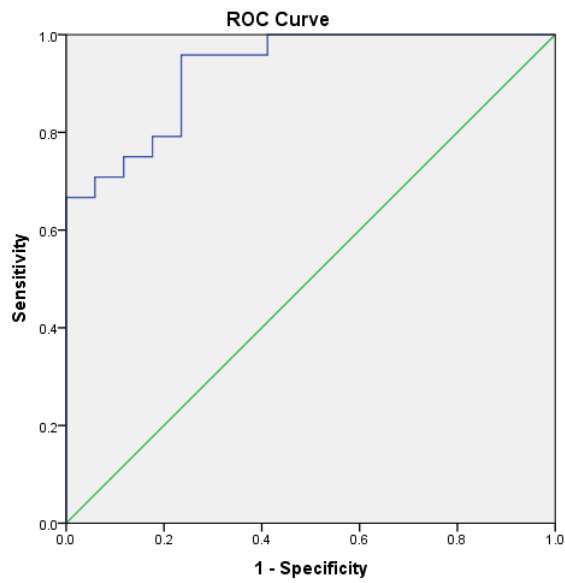|	Frequency	%
Sex		
Male	24	58.5
Female	17	41.5
Age		
Mean	$34,8 \pm 13,8$	
Median	36.0	
Range	18 – 74 years old	
Perforation of Appendic		
Perforated	24	58.5
Non-perforated	17	41.5
Total	41	100

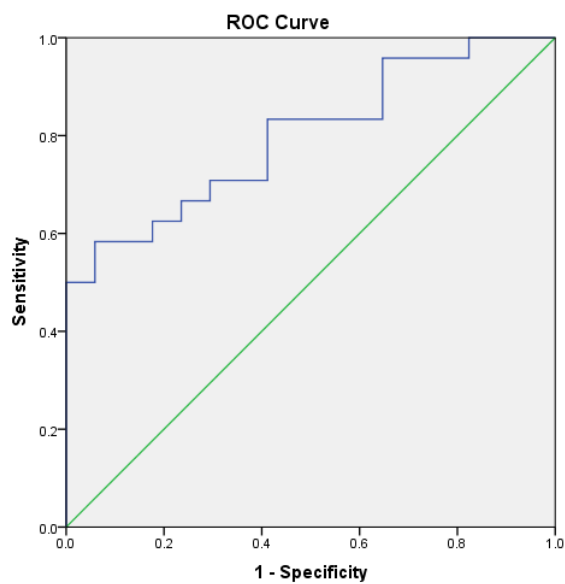**Figure 1.** ROC curve of D-Dimer level

Figure 2. ROC curve for CRP level

ARTIKEL PENELITIAN

Table 2. Accuracy of D-Dimer

		Appendicitis perforation	Appendicitis non perforation	Total	p
D-Dimer	≥0.51	23	4	27	<0,05
		95,8%	23,5%	65,9%	
	<0.51	1	13	14	
		4,2%	76,5%	34,1%	
Total		24	17	41	
		100,0%	100,0%	100,0%	

Table 3. Accuracy of CRP

		Appendicitis perforation	Appendicitis non perforation	Total	p
CRP	≥18.84	14	1	15	<0,05
		58,3%	5,9%	36,6%	
	<18.84	10	16	26	
		41,7%	94,1%	63,4%	
Total		24	17	41	
		100,0%	100,0%	100,0%	