

C-Reactive Protein and Leukocyte as Predictors of Complications in Peripheral Arterial Disease

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Abstract. Peripheral Arterial Disease (PAD) is the narrowing of peripheral blood vessels which prevalence is high in the elders. In 2010, it was estimated that 202 million people were suffering from PAD, most of which are in developing countries, especially the Southeast Asia region. Inflammation markers such as leukocyte and C-Reactive Protein (CRP) can predict the incidence of PAD but their use in determining prognosis remains unclear. Complications in PAD include amputation, increased cardiovascular events, and even death. Aim: This study aims to determine the relationship between leukocyte and CRP level on complications in PAD, in the forms of amputation, cardiovascular events, and mortality. Methods: This is a meta analysis study which uses online literature sourced from Pubmed, Science Direct, Cochrane, and Google Scholar. Results: Based on the data analysis, there is a significant relationship between CRP with the incidence of amputation (HR 1.24, 95%CI: 1.02-1.49, p=0.03) and hs-CRP with cardiovascular events (HR 1.33, 95%CI: 1.10-1.60, p=0.003). Leukocyte on the other hand shows no significant relationship with the incidence of amputation (OR 1.10, 95%CI: 0.98-1.23, p=0.10) and mortality (OR 1.14, 95%CI: 0.97-1.35, p=0.12)

Keyword: Peripheral Arterial Disease, Complication, Leukocyte, C-Reactive Protein

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1 Introduction

PAD is defined as partial or total narrowing of blood vessels in peripheral arteries which is most often caused by atherosclerosis¹. The location of the obstruction is often found in the lower extremities, affecting the popliteal artery, femoral artery and aortoiliac artery. There are several risk factors for PAD which include diabetes, hypertension, smoking, obesity, alcohol use, race, and Chronic Kidney Disease (CKD). Other important factors are increase in leukocyte, homocysteine, fibrinogen, and C-Reactive Protein levels².

As many as 202 million people worldwide experienced PAD in 2010 and in the study A Global Atherothrombosis Assessment by American Society of Cardiology in 2006, it was found that the prevalence of PAD in Indonesia was 9.7%. A multi-country study of Peripheral Arterial Disease – Screening and Evaluation of diabetic patients in Asian Regions Characterized by

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High Risk factors (PAD-SEARCH) said that there are 13.807 people affected by PAD for every one million people in Indonesia³.

The role of inflammation is very important in the pathophysiology of PAD. Apart from being potential risk factors for PAD, inflammatory markers such as CRP and fibrinogen are also mentioned can be used as progressivity, functional capacity and complications markers in PAD patients⁴. Therefore, the authors are interested in conducting a study of the role of C-Reactive Protein and leukocytes in predicting complications in PAD.

2 Methodology

This is a meta-analysis study using online publication studies from google scholar, pubmed, chocrane, and science direct by using the search phrase “(((*Leukocyte OR C-Reactive Protein*) *AND Peripheral Arterial Disease*) *AND Complication*)”. The purpose of this study is to determine the relationship between leukocyte and CRP levels on complications in PAD. Inclusion criterias are publications done in the last 10 years, and have levels of CRP and leukocyte which can be calculated to determine the size of effect (Odds ratio/Hazard ratio). Review articles, comments, and study conducted in animals are excluded in this study.

3 Result

A total of 11 studies that meets the inclusion criteria with three discussing the relationship between CRP and amputation, three discussing hs-CRP and Cardiovascular events, four discussing leukocyte and amputation, two discussing leukocyte and mortality. There is an overlap literatures between the studied subjects. Characteristics of the studies can be seen in table 1.

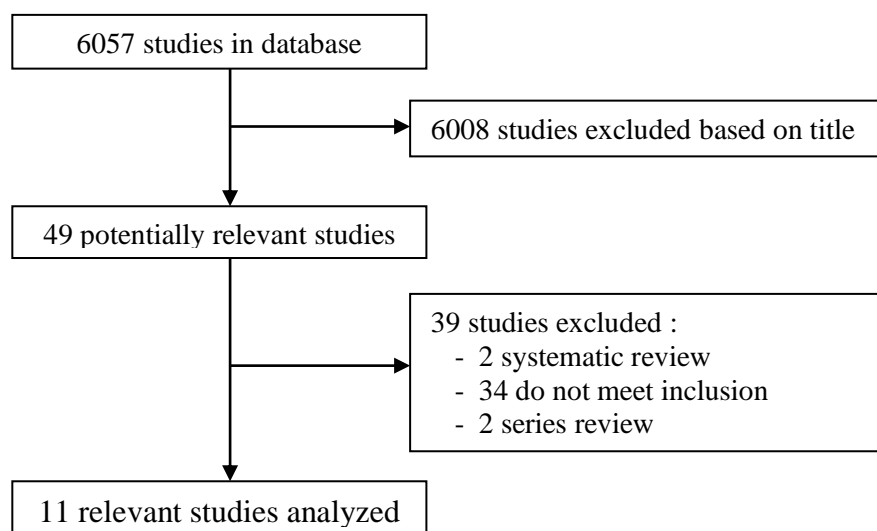


Figure 1 Selection of study used for meta-analysis.

Table 1 Study Characteristics.

Study	Sample	Endpoint	HR (95% CI)
Iida et al ⁵ . (2012)	406	Overall survival, limb salvage, reintervention	2.585 (1.251-5.341)
Shimamoto et al ⁶ . (2020)	3505	Incidence of MALE (Major Adverse Limb Events)	CRP ≥ 0.3 1.44 (1.20-1.74) CRP ≤ 0.3 1.12 (0.96-1.30)
Won et al ⁷ . (2014)	101	Reintervention, major amputation, minor amputation, and survival	1.06 (1.01-1.12)
Otaki et al ⁸ . (2017)	246	Major Adverse Cardiovascular Events (MACE)	1.36 (0.82-2.29)
Urbonaviciene et al ⁹ . (2012)	463	All cause mortality or Cardiovascular mortality.	CLI group 1.17 (0.85-1.62) IC group 1.22 (0.89-1.67)
Skoglund et al ¹⁰ . (2014)	188	Major Adverse Cardiovascular Events (MACE)	2.05 (1.29-3.27)
Study	Sample	Endpoint	OR (95% CI)
Amaranto et al ¹¹ . (2011)	1773	Death, Amputation, TIA, stroke, Bleeding, Infection, reoperation.	Endovascular 1.672 Openvascular 1.07
Lin et al ¹² . (2010)	85	Major Amputation	2.26 (0.45-11.3)
Saskin et al ¹³ . (2016)	123	Mortality and Amputation	1.00 (0.99-1.01)
Taşoğlu et al ¹⁴ . (2014)	104	Amputation and all-cause death	1.10 (0.90-1.2)
Bhutta et al ¹⁵ . (2011)	1021	Death within 2 years	1.02 (0.95-1.09)

3.1 CRP and hs-CRP

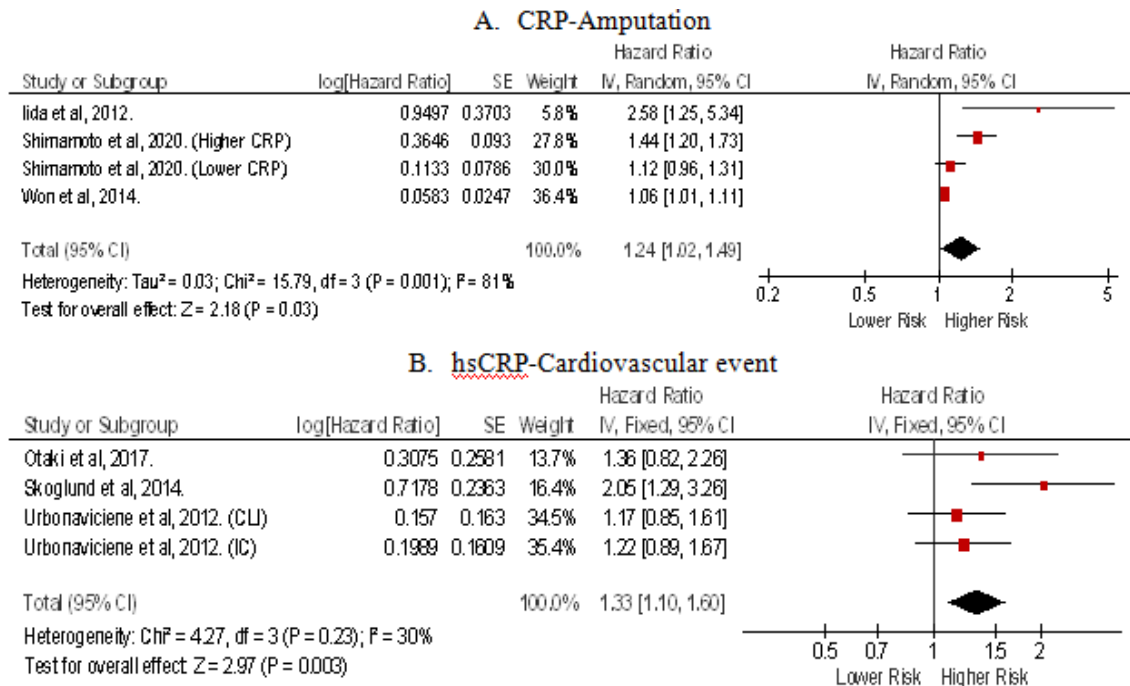


Figure 2 Forest plot A: CRP level and Amputation; Forest plot B: hs-CRP level and cardiovascular events.

Analysis of leukocyte and complication of PAD can be seen in Figure 2. The results of four combined data used from three different studies shows that increased level of CRP have a significant relationship with the incidence of amputation (Forest plot A). The total hazard ratio obtained is 1.24 with 95% confidence interval between 1.02 and 1.49 ($p=0.03$).

Hs-CRP level also correlates significantly with the incidence of cardiovascular events in PAD patients such as myocardial infarction, stroke, and all-cause cardiovascular death (Forest plot B) with total hazard ratio 1.33 and 95% confidence interval ranging from 1.10 to 1.60.

3.2 Leukocyte

Analysis of leukocyte and complication of PAD can be seen in Figure 3. In contrast to the two previous analyzes, no significant relationship between leukocyte level and amputation incidence in PAD patient (Forest plot C). Total odds ratio obtained from five different data is 1.10 with 95% Confidence Interval ranging from 0.98 to 1.23 ($p=0.10$).

There is also no significant relationship between leukocyte and mortality as one of the complication in PAD with total odds ratio 1.14 and 95% confidence interval ranging from 0.97 to 1.35 (Forest plot D).

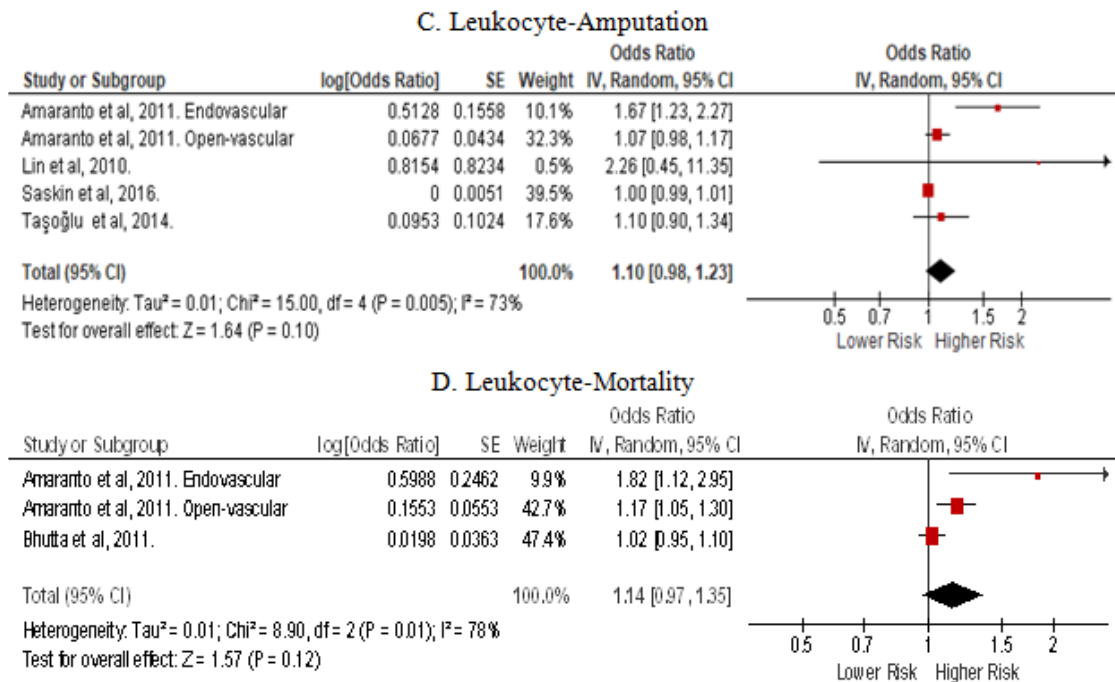


Figure 3 Forest plot C: Leukocyte level and amputation; Forest plot D: Leukocyte level and Mortality.

4 Discussion

Using three studies with 4012 total samples, we found a strong correlation between CRP level and the incidence of amputation ($HR=1.24$; 95%CI: 1.02-1.49, $p=0.03$). In Iida et al⁵ study, the mean CRP in the amputated group is 5.0 ± 5.1 mg/dL, higher than the non-amputated group with mean CRP 2.2 ± 3.6 mg/dL. Study by Shimamoto et al⁶ found 163 cases of amputation from a total of 2513 patients in the $CRP < 0.3$ group compared to 94 cases in the $CRP > 0.3$ group with a total of 993 samples.

Mean hs-CRP is also higher in patients with cardiovascular event as complication in PAD. Otaki et al⁸ in his study concluded that the mean hs-CRP in the group with cardiovascular event is significantly higher than in the uncomplicated group. The mean hs-CRP in the cardiovascular event group is 2.33 ± 0.65 pg/mL compared to 1.94 ± 0.54 pg/mL in the non-cardiovascular event group. In the meta-analysis, the total hazard ratio for cardiovascular event is at 1.33 (95%CI: 1.10-1.60, $p=0.003$).

Leukocyte level in the complicated group is higher than the uncomplicated group but shows no significant correlation^{11,15}. Total odds ratio found in the analysis is 1.10 (95%CI: 0.98-1.23, $p=0.10$) for the amputation outcome and 1.14 (95%CI: 0.97-1.35, $p=0.12$) for the mortality outcome.

5 Conclusion

In this study there is a significant correlation between CRP level and the incidence of amputation (HR=1.24, 95%CI: 1.02-1.49, p=0.03). There is also a significant correlation between hs-CRP level and cardiovascular events in PAD (HR=1.33, 95%CI: 1.10-1.60, p=0.003).

Unfortunately, we find no significant correlation between leukocyte and amputation in PAD (OR=1.10, 95%CI: 0.98-1.23, p=0.10) There is also no significant correlation between leukocyte and mortality in PAD (OR=1.14, 95%CI: 0.97-1.35, p=0.12)

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