ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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The Association Between Complete Blood Count and the Risk of Coronary Heart Disease

Tam Kan Sayımı ile Koroner Kalp Hastalığı Arasındaki İlişki

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ABSTRACT Objective: To determine the correlation between complete blood count and the risk of coronary heart disease (CHD). **Material and Methods:** All CHD patients treated in Aisyiyah Hospital during January 2011 to December 2017 were enrolled for the study. Information related to demographic, clinical, and complete blood count were extracted from medical record. Multiple logistic regression test was employed to evaluate the correlation between complete blood count and CHD incidence. In addition, a meta-analysis was also conducted to summarize findings from other regions. **Results:** A total of 516 CHD patients and 102 controls were included in our study. We found that elevated hemoglobin (OR 95%CI=4.92 [2.02-12.01], p=0.002), leukocyte (OR 95%CI=5.35 [3.17-9.03], p=0.001), hematocrit (OR 95%CI=2.31 [1.40-3.83], p=0.010), eosinophil (OR 95%CI= 2.78 [1.68-4.26], p=0.001), and monocyte (OR 95%CI=1.31 [0.80-2.16], p=0.023) were associated with the incidence of CHD. Furthermore, our meta-analysis revealed that elevated levels of leukocyte, eosinophil, and monocyte increased the risk of CHD approximately 3.57, 5.34, and 2.77 times, respectively. **Conclusion:** There is strong evidence that elevated levels of leukocyte, eosinophil, and monocyte are the risk factor for CHD.

Keywords: Complete blood count; coronary heart disease; risk factor

ÖZET Amaç: Tam kan ayımı ile koroner kalp hastalığı (KKH) arasında korelasyon olup olmadığını araştırmak amaçlandı. **Gereç ve Yöntemler:** Aisyiyah Hastanesi'nde Ocak 2011-Aralık 2017 arasında tedavi gören tüm KKH hastaları çalışma kapsamına alındı. Hastalarla ilgili demografik bilgiler, klinik veriler ve tam kan sayımları tıbbi kayıtlardan alındı. Aradaki bağlantıyı incelemek için multipl lojistik regresyon analizi yapıldı. KKH insidansı analizine ilaveten diğer yayınlardan elde edilen özet verilerin meta-analizi yapıldı. **Bulgular:** Toplam 516 KKH hastası ve 102 kontrol kişisi çalışmaya alındı. KKH insidansı ile ilişkili olarak hemoglobin (OR %95 GA=4,92 [2,02-12,01] p=0,002, lökosit (OR %95 GA=5,35 [3,17-9,03] p=0,001, hematokrit (OR %95 GA=2,31 [1,40-3,83] p=0,010, eozinofil (OR %95 GA=2,78 [1,68-4,26] p=0,001 ve monosit (OR %95 GA=1,31 [0,80-2,16] p=0,023 değerlerini yükselmiş olarak bulduk. Üstelik, yaptığımız meta-analize göre, KKH riskinde yükselmiş lökosit, eozinofil ve monosit değerlerinin yaklaşık 3,57; 5,34; ve 2,77 kat artma yarattığını saptadık (sırasıyla). **Sonuç:** KKH risk faktörü olarak yükselmiş lökosit, eozinofil ve monosit değerlerinin kuvvetli etkin olduğu tespit edilmiştir.

Anahtar Kelimeler: Tam kan sayımı; koroner kalp hastalığı; risk faktörü

Coronary heart disease (CHD) remains a serious health problem. The reports revealed that CHD has caused 11.2% global deaths. Although crude mortality rate for CHD remains stable, this number increases rapidly with age.[1-3] Atherosclerosis of coronary arteries, the main cause of CHD, is a complex inflammatory disorder that causes the changes in the cells of the arterial wall and the blood components.[4,5] Several inflammatory biomarkers such as troponin, C reactive protein (CRP), and B-type natriuretic peptide (BNP) or pro-BNP are used to stratify the risk of

CHD.[6] Moreover, a high-sensitivity CRP (hs-CRP) is one of the commonest predictor being used in predicting recurrent events, myocardial infarction, or restenosis after percutaneous coronary intervention.[7] However, its usage in developing country is not routinely performed because of the cost. In fact, most of deaths due to CHD occur in low- and middle-income countries.[1,2]

The complex interaction between endothelial cells, smooth muscle cells, leukocytes, and platelets has been known to have a pivotal role in inflammatory response in atherosclerosis.[8] This interaction has been proven by the previous studies, such as: elevated levels of leukocytes have long been known to correlate with an increased risk of death, aortic arch plaque thickness in CHD patients, aortic atheroma progression in stroke patient, and increased risk of mortality in patients with intracranial atherosclerotic disease.[8-11] Another study also revealed that elevated neutrophil levels were associated with increased the risk of major-adverse cardiac events in CHD patients.[12] In addition, other complete blood count components, such as hematocrit, platelet count, and erythrocyte sedimentation rate are also associated with the risk of CHD and the combination of leukocyte count with other complete blood count components could improve the ability to predict the risk of CHD.[13,14] Assessment of these blood components is inexpensive and widely available. Therefore, the aim of this study was to investigate the possibility of complete blood count as the predictor of CHD.

MATERIAL AND METHODS

STUDY DESIGNS AND PATIENTS

A retrospective study was conducted in Aisyiyah Hospital, Malang, Indonesia. The target population was all CHD patients treated in Aisyiyah Hospital during January 2011 to December 2017. The inclusion criteria were (1) suffered from CHD (the diagnosis of CHD was established according to standard protocol including anamnesis, physical examination, electrocardiogram, and laboratory findings) and (2) aged over 18 years. Patients with one of these clinical conditions (renal dysfunction (creatinine ≥1.5 mg/dL), hepatic disorder, concomitant inflammatory disease, neoplastic disease, systemic disorder, acute or chronic infectious disease, haematological disorder, and on medications which could affect complete blood count) were excluded. Information related to gender, age, diagnosis, body mass index, mean arterial blood pressure, the level of blood glucose, low-density lipoprotein (LDL), urea and creatinin and complete blood count was extracted from medical record. We used total sampling method. Controls were obtained from healthy and or non-CHD individuals with age-and gender-matched recorded in Aisyiyah Hospital. Our study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki. Informed written consent was waived because our study was a retrospective.

STUDY VARIABLES

In our study, the response variable was the incidence of CHD. While, the explanatory variables were hematocrit (%), concentration of hemoglobin (g/dl), and the levels of erythrocyte, leukocyte, thrombocyte, eosinophil, basophil, neutrophil, monocyte, and lymphocyte (cell/μL). Those variable measurements, measured using XS-800i Hematology Analyzer (Sysmex Europe GmbH, Norderstedt, Germany), were retrieved from medical record.

STATISTICAL ANALYSIS

The association between complete blood count and the risk of CHD was analyzed using multiple logistic regression. Statistically significant was considered if the p value was less than 0.05. We used the Statistical Package of Social Sciences 17.0 software (SPSS Inc., Chicago, IL) to analyze the data.

META-ANALYSIS DESIGN

We also performed a meta-analysis to investigate the correlation between complete blood count and the risk of CHD. The approach of meta-analysis was adapted from the previous studies.[15,16] Briefly, we collected articles concerning the correlation between complete blood count and the risk of CHD to calculate the pooled odd ratios (ORs) and (5% confidence intervals (95%CIs).

ELIGIBILITY CRITERIA AND DATA EXTRACTION FOR META-ANALYSIS

The inclusion criteria for this study were: (1) studies with the following designs: retrospective, prospective, cross-sectional, randomized-controlled trials (RCTs), controlled before-and-after studies, and cross-over studies; (2) investigating the correlation between complete blood count and the risk of CHD; and (3) providing sufficient data to calculate OR 95% CI. We extracted the following information from each study: (1) name of the first author; (2) year of publication; (3) country of origin; (4) sample sizes of cases and controls, and (5) levels of blood cells count.

SEARCH STRATEGY AND LITERATURE FOR META-ANALYSIS

We searched published articles up to June 20th, 2018 in PubMed and Embase with no language restrictions. For searching stategy, we used the combination of the following key words: (complete blood count or CBC or hematocrit or hemoglobin or erythrocyte or leukocyte or thrombocyte or eosinophil or basophil or neutrophil or monocyte or lymphocyte) and (coronary artery disease or coronary heart disease or ischemic heart disease or myocardial infarct (MI) or CHD or CAD or IHD or MI or angina). The publication languages were limited to English.

STATISTICAL ANALYSIS FOR META-ANALYSIS

The correlation between complete blood count and the risk of CHD was determined by calculating pooled ORs and 95% CIs. We used Z-tests to estimate the significance of pooled ORs (statistically significant was considered if the p value was less than 0.05). For evaluating the heterogeneity, we used a Q-test. We used a random effects model to calculate the OR 95% CI if heterogeneity existed (P<0.10). While, if heterogeneity was not existed, we used a fixed effects model. Moreover, we used Egger's test to evaluate the publication bias (statistically significant was considered if the p value was less than 0.05). For all statistical testing in our meta-analysis, we used a Comprehensive Meta-analysis (CMA, New Jersey, USA) 2.0 software to analyze the data.

RESULTS

CHARACTERISTICS OF PATIENTS

A total of 516 CHD patients and 102 controls were analyzed. The average age of the CHD patients were 59.5 (±12.32) years old with the average of body mass index (BMI) was 25.12 (±3.82 kg/m2) (Table 1). Other baseline characteristics of the patients such as mean arterial blood pressure and the level of blood glucose, LDL, urea, and creatinine are presented in (Table 1). The data showed no significant different between case and control. This indicated that the data was homogeneous.

ASSOCIATION BETWEEN COMPLETE BLOOD CELLS COUNT AND CHD

The average number of complete blood cells count in 516 CHD patients are presented in (Table 2). We found that the elevated levels of hemoglobin, leukocyte, hematocrit, eosinophil, and monocyte

TABLE 1: Baseline characteristic of case and control included in the study.

	Mean ± SD		
Characteristic	**Case (n=516)**	**Control (n=102)**	**p**
Age (years)	59.50 ± 12.32	58.62 ± 16.31	0.083
Body mass index (kg/m^2)	25.12 ± 3.82	24.28 ± 4.35	0.061
Mean arterial blood pressure (mmHg)	112.86 ± 16.68	115.69 ± 22.53	0.127
Blood glucose (mg/dl)	158.63 ± 79.64	164.86 ± 60.07	0.473
Low density lipoprotein (mg/dl)	116.53 ± 28.87	118.62 ± 25.33	0.516
Urea (mg/dl)	33.32 ± 28.83	34.28 ± 22.17	0.741
Creatinine (mg/dl)	1.12 ± 0.66	1.18 ± 0.54	0.388

SD: standard deviation.

were associated with the risk of CHD (Table 2). While, other components of blood cells count such as erythrocyte, thrombocyte, basophil, neutrophil, and lymphocyte had no significant association with the risk of CHD.

META-ANALYSIS

Based on the search strategy, we identified 56 962 potentially relevant papers. Of those, by reading their titles and abstracts, we excluded 56 943 papers because of irrelevance. Moreover, by reading the full texts, we excluded three papers because of reviews; ten papers because of no sufficient data; and another paper because of study bias. Figure 1 displays the flowchart of inclusion process in our study. Totally, we included five studies in the meta-analysis.

We found some studies have been conducted previously to assess the correlation between the complete blood count and CHD. Details were as follows: seven studies concerning the correlation between hematocrit and CHD, five studies concerning the association between hemoglobin and CHD, 16 studies concerning the association between leukocyte and CHD, eight studies concerning the correlation between eosinophil and CHD, and four studies concerning the association between monocyte and CHD.[17,22-46] Of those; only leukocyte, eosinophil and monocytes were compatible for meta-analysis.

We found 16 papers evaluating the correlation between leukocyte and the risk of CHD; seven retrospective studies, four cross sectional studies, four cohort studies, and one meta-analysis study. Of 16 studies, five studies were compatible for meta-analysis with a total of 889 CHD patients and 4306 controls (Table 3).[22,29-43]

TABLE 2: The average number and standard deviation of complete blood count in the study.

	Mean (±SD)			
Complete blood count	**Cases (n = 516)**	**Controls (n = 102)**	**OR [95%CI]**	***p***
Hemoglobin (g/dL)	13.86 ± 1.52	12.33 ± 1.78	4.92 [2.02 - 12.01]	0.002
Erythrocytes (cell/µL)	4.74 ± 0.72	4.48 ± 0.62	2.10 [0.88 - 5.03]	0.097
Leukocytes (cell/µL)	8805.12 ± 3019.03	5174.58 ± 936.57	5.35 [3.17 - 9.03]	0.001
Hematocrit (%)	40.63 ± 4.58	38.23 ± 5.74	2.31 [1.40 - 3.83]	0.010
Thrombocytes (cell/µL)	268.20 ± 58.04	268.02 ± 62.86	1.00 [0.99 - 1.02]	0.640
Eosinophils (cell/µL)	0.18 ± 0.22	0.08 ± 0.12	2.78 [1.68 - 4.62]	0.001
Basophils (cell/µL)	0.03 ± 0.12	0.02 ± 0.08	1.19 [0.73 - 1.97]	0.484
Neutrophils (cell/µL)	6.84 ± 4.43	4.93 ± 0.62	2.99 [1.80 - 2.16]	0.314
Monocytes (cell/µL)	0.72 ± 0.28	0.68 ± 0.25	1.31 [0.80 - 2.16]	0.023
Lymphocytes (cell/µL)	1.68 ± 0.53	1.66 ±0.64	1.06 [0.65 - 1.75]	0.808

Note: SD: standard deviation; OR: Odds ratio; 95% CI: 95% confidence interval.

TABLE 3: Summary of meta-analysis regarding the association between blood cell count and the risk of CHD.

No.	CHD vs. control	OR	95%CI	p	pH	pE
1.	Leukocytes	3.57	1.84-6.93	0.0001	0.0001	0.766
2.	Eosinophils	5.34	1.17-24.77	0.0310	0.0001	1.034
3.	Monocytes	2.77	2.11-3.64	0.0001	0.1220	0.150

CHD: Coronary heart disease; OR: odds ratio; 95%CI: 95% confidence interval; pH: p heterogeneity; pE: p Egger.

We found that elevated leukocyte had a significant association with the incidence of CHD (OR 95%CI=3.57 [1.84-6.93], p<0.001) (Table 3, Figure 2 A).

For the association between eosinophil and CHD, eight studies were identified; four retrospective studies, three cross sectional studies and one cohort study.[30,38-40,43-46] Of these, five studies and our results with a total 513 CHD patients and 3998 controls were included in our meta-analysis.[30,38-40,43] The results found that elevated eosinophil count had the significant association with the risk of CHD (OR 95%CI = 5.34 [1.17-24.77], p=0.031) (Table 3, Figure 2 B). Four previous studies evaluating the correlation between monocyte count and the risk of CHD were identified.[30,38,39,47] Of these studies, three studies combined with our study with a total of 393 CHD patients and 3871 controls were included in our meta-analysis.[30,38,39] The result revealed that elevated monocyte was correlated with the risk of CHD (OR 95%CI=2.77 [2.11-3.64], p<0.001) (Table 3, Figure 2 C).

Evidence for heterogeneity was found in eosinophil and leukocyte (P<0.001) and therefore, data was analyzed using random effects model. Using Egger test, we found no publication bias (P>0.05). Forest plots the association between [leukocyte, eosinophil, and monocyte] and [the risk of CHD] are presented in (Figure 2 A-C).

DISCUSSION

Atherosclerosis, the main cause of CHD, is a multifactoral disease that involves chronic inflammation at every stage.[48] The inflammation process in atherosclerosis is a complex, and consist of several steps.[49] Complete blood count has been proven to be associated with inflammation and here we reported the association between complete blood count and CHD.[50] Our report is the first study conducted to assess the association between complete blood count and CHD in Indonesia. The first study was conducted in Japan.[17] Basically, the concept of this study is similar to the previous studies and

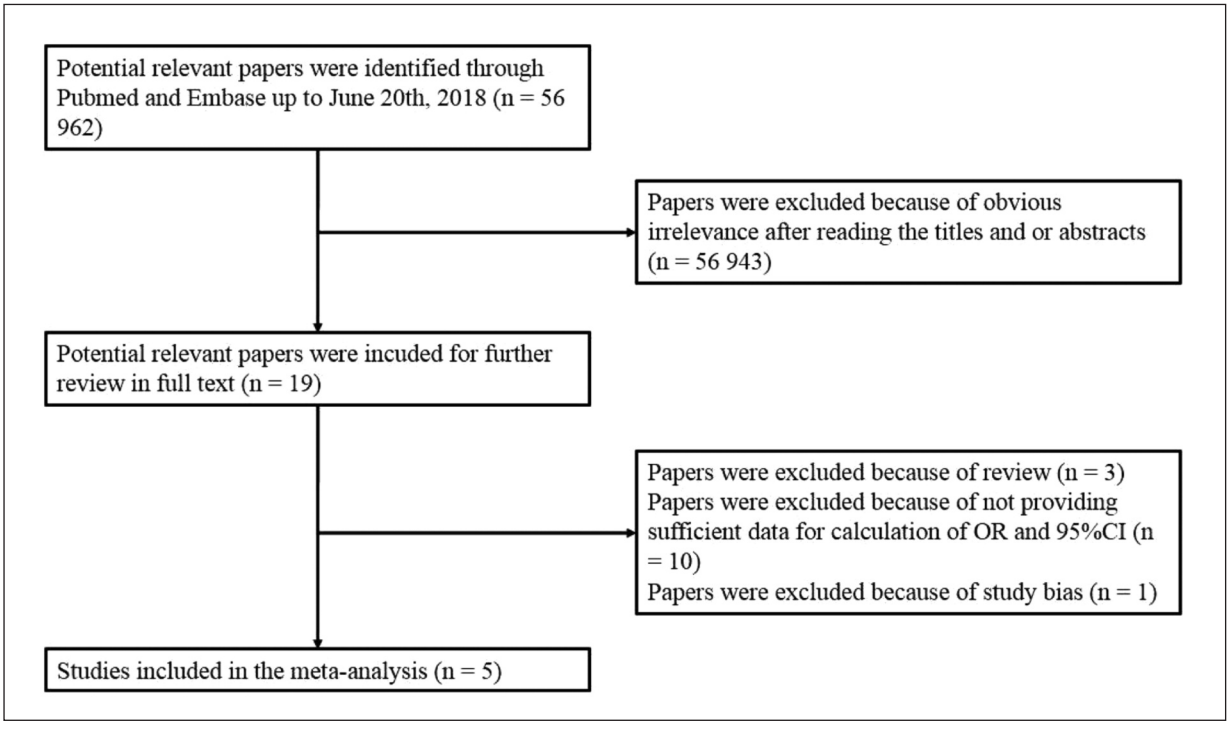

FIGURE 1: Selection of articles for inclusion in meta-analysis.

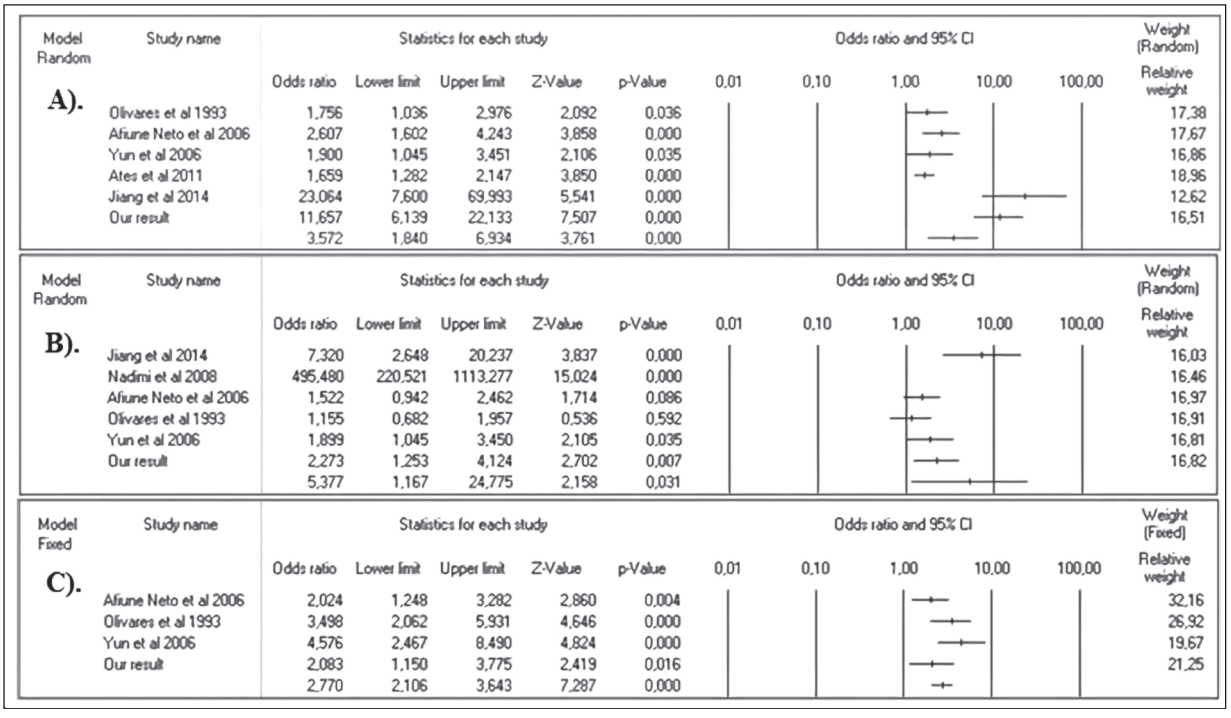

FIGURE 2: Forest plot regarding the association between leukocytes (A), eosinophils (B), monocytes (C) and the risk of CHD (cases vs. controls).

therefore our results are expected to be able to be used as the comparison.

Several studies have shown that leukocytosis is an independent risk factors of CHD.[8,40] There are several theories that explain the role of leukocytes in CHD. Leukocytes cause vascular injury through several ways, including damage to the endothelial cells caused by proteolytic and oxidative, plug the microvasculature through binding to the ischemic endothelium via the leukocyte integrin CD 11b/CD18, induce hypercoagulability by increased expression of tissue factor on leukocyte, promote infarct expansion by releasing pro-inflammatory cytokines, and destabilize of coronary artery plaques.[51,52,54-56]

Our study revealed that leukocytes count increased the risk of CHD by 5.35. Although these results indicated very small impact, our meta-analysis revealed that elevated leukocyte increased the odds of having CHD by 3.57 times (OR 95%CI= 3.57 [1.84-6.93], P<0.001). A previous meta-analysis also found that there was a significant association between leukocyte and the risk of CHD (OR 95%CI: 1.33 [1.17-1.50] P=0.001.[37]

Studies have identified that increased levels of almost all leukocyte sub-types, including monocytes, eosinophils, neutrophils, and lymphocytes were associated with increased risk of CHD.[39,45,57,58] We identified eight studies that have been conducted to assess the correlation between eosinophils count and the risk of CHD. Two retrospective studies and three cross sectional studies showed that there was a significant correlation between eosinophil count and the risk of CHD, but other studies found no association.[30,38-40,43-46] Our retrospective study and meta-analysis found that eosinophil count had the significant association with the risk of CHD.

The mechanism how eosinophils involved in CHD pathogenesis is still unclear. However, the interaction between eosinophils, platelets, and endothelium has the important role in thrombosis. Several studies have suggested the possible mechanism of eosinophils in thrombosis. First, eosinophils granules activate platelets and as the result, larger and hyper-reactive platelets accelerate the formation of thrombin.[59] Second, eosinophils synthesis and release some bioactive mediators, such as

leukotriene C4, histamine, and prostaglandin D2 from mast cells and basophils. These bioactive mediators are though to have an important role in cardiovascular system.[60] Third, degranulating eosinophils release toxic cationic protein that is a cytotoxic property in CHD.[60] This toxin stimulates the formation of mural thrombin throught binding to anion-binding exosite of thrombomodulin.[61] As a result, thrombomodulin is unable to form thrombomodulin-thrombin complex, a potent inhibitor of coagulation, and therefore it loses antithrombotic role.[62]

Several studies found that monocytes have pivotal roles in the pathogenesis of CHD.[30,38,39,47] A cohort study and three retrospective studies found that elevated monocyte count had the significant association with the risk of CHD.[30,38,39,47] These results were consistent with our study. Our meta-analysis also indicated that elevated monocyte was a risk factor for CHD. Monocytes have central role for plaque development in CHD patient.[63] Monocytes are short – lived cells, and do not proliferate in the blood. The functions of monocytes in homeostatic conditions are involved in scavenging dead cells and toxic molecules. Monocytes also have a pivotal role in the renewal of resident tissue macrophages and dendritic cells.[64]

During atherosclerosis, monocytes are recruited into intima and subintima through the luminal endothelium and interact with the endothelial adhesion molecule via specific integrin receptors macrophage adhesion ligand-1 (Mac-1).[64-66] This process is facilitated by platelets that secrete factors influencing the monocyte-macrophage phenotype.[65] In intima, monocytes phagocytose toxic molecules such as oxidized LDL through their scavenger receptors. Furthermore, monocytes produce inflammatory cytokines and differentiate into dendritic cells, macrophages or foam cells.[64]

There were several limitations in the study. First, in this study did not include data regarding the factors associated with CHD such as smoking, physical activity, and non modifiable factors of CHD. Second, we have no data concerning cardiac end point. Therefore, the severity levels of CHD could not be measured. Third, false negative results might be occurred in this study due to the small sample size. Therefore, further studies involving a larger sample size are required to determine the actual association. Fourth, the study regarding the association between complete blood count and the risk of CHD is very limited. Therefore, we could not perform meta-analysis on all complete blood count components.

CONCLUSION

In conclusion, our study indicates that elevated leukocytes, hemoglobin, hematocrit, eosinophils, and monocyte are correlated with the incidence of CHD in our population. Our meta-analysis reveals the evidence that leukocyte, eosinophil, and monocyte are the risk factor for CHD.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Jonny Karunia Fajar, Aditya Indra Mahendra;* ***Design:*** *Jonny Karunia Fajar;* ***Control/Supervision:*** *Teuku Heriansyah, Mohammad Saifur Rohman;* ***Data Collection and/or Processing:*** *Jonny Karunia Fajar, Aditya Indra Mahendra, Fredo Tamara, Bagus Aulia Mahdi;* ***Analysis and/or Interpretation:*** *Jonny Karunia Fajar, Aditya Indra Mahendra;* ***Literature Review:*** *Jonny Karunia Fajar, Aditya Indra Mahendra, Fredo Tamara, Bagus Aulia Mahdi;* ***Writing the Article:*** *Jonny Karunia Fajar, Aditya Indra Mahendra, Fredo Tamara, Bagus Aulia Mahdi;* ***Critical Review:*** *Teuku Heriansyah, Mohammad Saifur Rohman;* ***Materials:*** *Teuku Heriansyah, Mohammad Saifur Rohman.*

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