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Elevated Hemoglobin and Hematocrit are Associated with the Risk of Coronary Heart Disease

Yükselmiş Hemoglobin ve Hematokrit Düzeyi Koroner Kalp Hastalığı Riski ile İlişkilidir

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ABSTRACT

Objective: Hemoglobin and hematocrit tests are routinely performed. However, they are often ignored for evaluation of coronary heart disease (CHD) patients. The aim of this study is to compare hemoglobin and hematocrit levels between CHD patients and healthy individuals.

Materials and Methods: During January to June 2016, a retrospective was conducted in Aisyiyah Hospital, Malang, Indonesia. The following information was extracted from medical record, i.e.: gender, age, diagnosis, level of hematocrit, and hemoglobin. We analyzed the data using multiple logistic regression test.

Results: We compared level of hematocrit and hemoglobin of 133 CHD patients and 50 controls. Our results showed that elevated hemoglobin [odds ratio (OR) 95% confidence interval (CI)=20.80 (2.65-163.02), p=0.004] and hematocrit [OR 95% CI=2.17 (1.11-4.25), p=0.024] were associated with the risk of CHD.

Conclusion: Hemoglobin and hematocrit are associated with the risk of CHD.

Keywords: Coronary heart disease, hemoglobin, hematocrit

ÖZ

Amaç: Hemoglobin ve hematokrit testleri rutin olarak uygulanmaktadır. Bununla birlikte, koroner kalp hastalığı (KKH) olan hastaların değerlendirilmesinde sıklıkla göz ardı edilmektedir. Bu çalışmanın amacı KKH hastaları ve sağlıklı bireyler arasında hemoglobin ve hematokrit seviyelerinin karşılaştırılmasıdır.

Gereç ve Yöntemler: Ocak-Haziran 2016 süresince, Endonezya Malang'da Aisyiyah Hastanesi'nde retrospektif bir çalışma yürütüldü. Cinsiyet, yaş, tanı, hematokrit ve hemoglobin seviyesi gibi bilgiler tıbbi kayıtlardan toplandı. Veriler, çoklu lojistik regresyon testi kullanılarak analiz edildi.

Bulgular: KKH'si olan 133 hastanın ve 50 kontrolün hematokrit ve hemoglobin seviyeleri karşılaştırıldı. Bulgularımız, yükselmiş hemoglobin [odds oranı (OR) %95 güven aralığı (GA)=20,80 (2,65-163,02), p=0,004] ve hematokritin [OR %95 GA=2,17 (1,11-4,25), p=0,024] KKH riski ile ilişkili olduğunu göstermiştir.

Sonuç: Hemoglobin ve hematokrit, KKH riski ile ilişkilidir.

Anahtar kelimeler: Koroner kalp hastalığı, hemoglobin, hematokrit

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INTRODUCTION

Over the past decade, there has been an increase in mortality rates due to coronary heart disease (CHD) (1). This mortality rate is around 7.2 million in 2008 (2) and 7.4 million in 2015 and is predicted to reach 23.6 million in 2030 (3). The most mortality caused by CHD is sudden death (4). Therefore, the rapid and accuracy diagnosis are the keys to prevent CHD mortality.

Atherosclerosis is the most responsible for CHD (5). Atherosclerosis is a complex involving various pathways including inflammation, lipid modification, and red blood cell aggregation (6-8). It was disclosed that hemoglobin is atherogenic that has been linked to lipid modification and hematocrit has also been associated to red blood cells aggregation that triggers atherosclerosis (6,7). Correlation between elevated hemoglobin and lipid modification has been revealed by Salonen et al., Ziouzenkova et al., and Nagy et al. (9-11). Moreover, Gustafsson et al. and Dintenfass had shown that elevation of blood viscosity, which is the impact of elevated hematocrit has an important role in red blood cells aggregation (12,13). Therefore, it can be argued that theoretically hemoglobin and hematocrit levels likely have a correlation with the risk of CHD and possibly could be as an evaluation for CHD patients.

In our country, hemoglobin and hematocrit tests are routinely performed in hospitalized patients. These tests are often ignored for evaluation of CHD patients. However, they theoretically have an important role in the pathogenesis of CHD. Therefore, this study aimed to compare hemoglobin and hematocrit levels between CHD patients and healthy individuals.

MATERIALS AND METHODS

Study Designs and Patients

This study was a retrospective study conducted at Aisyiyah Hospital from January to June 2016. The total population was all CHD patients treated in Aisyiah Hospital during January 2011-December 2015 (610 patients-updated January 7th, 2016). Informed written consent was waived because the study was a retrospective data analysis. This study was approved by local ethical committee. A simple random sampling method was used to select 610 CHD patients. Totally, 133 CHD patients and 50 controls were included in the study.

Eligibility Criteria and Data Extraction

The inclusion and exclusion criteria in this study were determined carefully and gradually. Inclusion criteria for this study were (1) suffered from CHD and (2) aged over 18 years. The exclusion criteria were 1) renal dysfunction (creatinine ≥1.5 mg/dL), 2) hepatic disorder, 3) concomitant inflammatory disease, 4) neoplastic disease, 5) systemic disorder, 6) acute or chronic infectious disease, 7) haematological disorder, and 8) on medications which could affect complete blood count. Data extracted from the medical records included gender, age, diagnosis, body mass index, mean arterial blood pressure, the level of blood glucose, low-density lipoprotein (LDL), urea, creatinine, hemoglobin, and hematocrit.

Study Variables

Response variable: The response variable in this study was risk of CHD. CHD is a degenerative and inflammatory process that begins within the blood vessel wall, causing it to weaken, enlarge, and eventually impair blood flow through the damaged artery (14). In our hospital, CHD is diagnosed using clinical characteristics, electrocardiogram, and or angiography. The measurement results of this variable were increased or decreased risk of CHD. The data were obtained from medical record. Ordinal scale was used to assess this variable.

Explanatory variables: The explanatory variables in this study were the number of hemoglobin (g/dL) and hematocrit (%). The numbers of those components were extracted from medical record. All variable were in ratio scale. Data were recorded on the first day of admission.

Statistical Analysis

Data of odds ratio (OR) and 95% confidence interval (CI) regarding the association between hemoglobin and hematocrit levels with the risk of CHD were analyzed using multiple logistic regression test using SPSS software. The value $p<0.05$ was considered significant statistically.

RESULTS

A total of 133 of 610 CHD patients were selected for the study using random numbers. Of these, 35 patients were excluded because had renal dysfunction (8 patients), had hepatic disorder (2 patients), suffered neoplasm (11 patients), and suffered infectious disease (14 patients). The selection was continued to get 35 patients more. Controls

were obtained from non-CHD patients in Aisyiyah Hospital.

A total of 133 CHD patients and 50 controls were recruited for the study. The average age and standard deviation (SD) of CHD patients were 59.5±11.2 years old, the average body mass index and SD of CHD patients were 26.1±3.6 kg/m^2, the average mean arterial blood pressure and SD of CHD patients were 100.9±18.9 mmHg, the average blood glucose and SD of CHD patients were 154.6±82.7 mg/dL, the average LDL and SD of CHD patients were 106.3±26.6 mg/dL, the average urea and SD of CHD patients were 34.4±29.4 mg/dL, the average creatinine and SD of CHD patients were 1.4±0.8 mg/dL (Table 1). The average level of hemoglobin and hematocrit were summarized in Table 2. The study found that haemoglobin [OR 95% CI=20.80 (2.65-163.02), p=0.004] and hematocrit [OR 95% CI=2.17 (1.11-4.25), p=0.024] were associated with the risk of CHD. Table 3 summarized OR and 95% CI regarding the association between hemoglobin and hematocrit with the risk of CHD.

Table 1: Patients' characteristic included in the study

Subgroup		Mean ± SD						
		Age	BMI	MAP	BG	LDL	UR	CR
All		59.5±11.2	26.1±3.6	100.9±18.9	154.6±82.7	106.3±26.6	34.4±29.4	1.4±0.8
Gender	M	58.7±11.8	25.7±3.4	103.6±19.5	156.7±84.7	103.6±24.9	34.6±32.1	1.2±0.8
	F	61.8±9.2	27.1±4.0	94.4±15.9	148.8±77.9	117.5±29.7	33.9±22.1	0.9±0.4
CEP	MI	58.9±10.9	26.2±3.4	103.4±19.5	158.7±85.5	108.1±3.4	35.5±38.1	1.2±1.0
	UAP	58.4±12.5	26.2±3.9	97.4±17.9	155.6±87.7	105.0±30.0	28.9±17.8	0.9±0.3
	AP	61.3±8.4	26.2±4.1	105.5±19.5	127.4±59.9	103.0±7.0	34.8±18.8	1.1±0.5
	CHDu	65.2±9.2	25.1±3.2	99.2±18.0	156.8±77.1	117.2±35.6	48.9±26.9	1.3±0.6
OC	I	59.2±11.2	26.1±3.4	101.2±19.4	149.2±79.2	108.1±25.7	34.1±30.3	1.4±0.7
	NI	62.4±10.8	24.2±4.5	104.3±15.8	180.7±110.5	113.0±60.8	36.5±13.9	1.2±0.6
	D	64.3±10.1	27.1±5.9	92.0±11.7	254.5±78.5	94.7±28.2	36.2±25.9	1.2±0.4

SD: Standard deviation, BMI: Body mass index (kg/m^2), MAP: Mean arterial blood pressure (mmHg), BG: Blood glucose (mg/dL), LDL: Low-density lipoprotein (mg/dL), UR: Urea (mg/dL), CR: Creatinine (mg/dL), M: Male, F: Female, CEP: Cardiac end points, MI: Myocardial infarction, UAP: Unstable angina pectoris, AP: Angina pectoris, CHDu: Coronary heart disease unspesified, OC: Outcome, I: Improved, NI: Not improved, D: Death

Table 2: The average number and standard deviation of the study

Subgroup		Mean ± SD	
		Hemoglobin (g/dL)	Hematocrit (%)
All	Case	13.5±1.6	39.6±4.6
	Control	12.3±1.7	37.3±4.9
Gender	Male	13.9±1.6	40.4±4.5
	Female	12.6±1.3	37.6±4.1
Cardiac end point	Myocardial infarction	13.8±1.6	40.3±4.5
	Unstable angina pectoris	13.6±1.4	39.9±4.1
	Stable angina pectoris	13.1±1.7	38.3±4.7
	Coronary heart disease unspecified	12.5±1.9	36.9±5.4
Outcome	Improved	13.4±1.6	39.5±4.5
	Not improved	13.5±1.6	39.1±4.4
	Death	14.3±1.5	42.0±4.9

SD: Standard deviation

Table 3: Summary of odds ratio and 95% confidence interval regarding the association between blood cells count and the risk of coronary heart disease

Parameters	Sub group analysis	OR	95% CI	p
Hemoglobin	Case vs control	20.80	2.65-163.02	0.004
	Gender	0.16	0.04-0.59	0.006
	Cardiac end point	0.43	0.15-1.26	0.125
	Outcome	2.18	0.42-11.39	0.354
Hematocrit	Case vs control	2.17	1.11-4.25	0.024
	Gender	1.59	1.05-2.40	0.028
	Cardiac end point	1.04	0.74-1.46	0.828
	Outcome	0.85	0.50-1.45	0.550

OR: Odds ratio, CI: Confidence interval

DISCUSSION

Atherosclerosis has an important role in CHD pathogenesis (15). The inflammation process in atherosclerosis is a complex, involving lipid modification and red blood cells aggregation that theoretically could be triggered by elevated hemoglobin and hematocrit (6,7). This study reported the comparison of hemoglobin and hematocrit levels between CHD patients and healthy individuals.

Our results found that hemoglobin counts was 20.08 fold associated with the risk of CHD. This result was consistent with several studies. Totally, there were five studies regarding the association between hemoglobin and the risk of CHD we collected from Pubmed and EMBASE (Table 4). However, data were not compatible for a meta-analysis. Therefore, we compared our data narratively. Two retrospective studies conducted by Chonchol and Nielson in US population and Shah et al. in UK population showed that hemoglobin had significant association with the risk of CHD, with OR 95% CIs were 1.22 (1.08-1.37), p=0.0001 and 2.00 (1.76-2.29), p=0.0010, respectively (16,17). Furthermore, in cross sectional models, three studies had shown that hemoglobin was associated with the risk of CHD in US (18), India (19), and Turkey population (20). Overall, many studies including our study showed that hemoglobin levels were significantly associated with increased risk of CHD. In addition, correlated to gender, our findings showed that hemoglobin in male was higher than in female (Table 1). However, we could not make a conclusion regarding the association between hemoglobin levels in CHD and gender, because hemoglobin in men and women has different normal values. Moreover, our results showed that hemoglobin had no significant correlation to the cardiac end points and outcomes. Nevertheless, there was a trend towards cardiac endpoints that include myocardial infacrtion, unstable angina pectoris, angina pectoris, and CHD unspecified having a synergistic average of hemoglobin levels, i.e.; 13.8 (±1.6), 13.6 (±1.4), 13.1 (±1.7), and 12.5 (±1.9), respectively. This showed that the higher the hemoglobin level the higher the severity (Figure 1).

A study (16) found that the lower or higher hemoglobin was associated with the risk of CHD. While, our finding revealed that elevated hemoglobin level was associated with the risk of CHD. Therefore, we restricted our discussion only concerning the correlation between elevated hemoglobin and the risk of CHD. Theoretically, the association between hemoglobin concentration and the risk of CHD has not been fully understood. In association with atherosclerosis, the high level of hemoglobin is a reflection the increase of oxidative stress. This leads to weakness of nitride oxide activity and causes oxidative modification of LDL (21). An atherogenicity theory explains that native LDL does not cause accumulation of intracellular lipids, but modified LDL is atherogenic, causing accumulation of lipid in arterial cells and transforming them into foam cells. On the other hand, autoantibodies against modified LDL is also responsible for atherosclerosis (22). In addition, elevated hemoglobin may be taken up by HDL-C particle, thereby changing anti atherogenic property of HDL-C to become pro

Table 4: Summary of the comparison of the study with other several studies regarding the association of absolute blood cells count with the risk of coronary heart disease

First author name and year	Sample size	Age (y)	Population	Design	OR	95% CI		p
Hemoglobin								
Sabatine et al. (18)	25419	60.2	US	Cross sectional	1.79	1.18	2.71	0.0070
Chonchol and Nielson (16)	25622	NA	US	Retrospective	1.22	1.08	1.37	0.0001
Padmanaban and Toora (19)	50	52.0	India	Cross sectional	NA	NA	NA	0.0001
Shah et al. (17)	20131	64.1	UK	Retrospective	2.00	1.76	2.29	0.0010
Doganer et al. (20)	356	NA	Turkey	Cross sectional	3.08	NA	NA	0.0110
Our results	133	59.5	Indonesia	Retrospective	20.80	2.65	163.02	0.0040
Hematocrit								
Carter et al. (29)	8006	NA	Japan	Cohort	NA	NA	NA	0.058
Gotoh et al. (30)	2585	59.3	Japan	Cohort	1.80	1.16	2.70	0.008
Gagnon et al 1994	5209	NA	Mix	Cohort	NA	NA	NA	0.028
Zhong et al. (28)	33623	NA	Europe	Retrospective	1.07	1.03	1.11	< 0.050
Kunnas et al. (27)	670	55	Finland	Retrospective	1.80	1.10	2.70	< 0.050
Brown et al. (31)	8896	49.8	USA	Cohort	1.30	0.90	1.90	< 0.050
Sorlie et al. (32)	8706	NA	Puerto Rico	Cohort	NA	NA	NA	0.0260
Our results	133	59.5	Indonesia	Retrospective	2.17	1.11	4.25	0.0240

NA: Not available, OR: Odds ratio, CI: Confidence interval

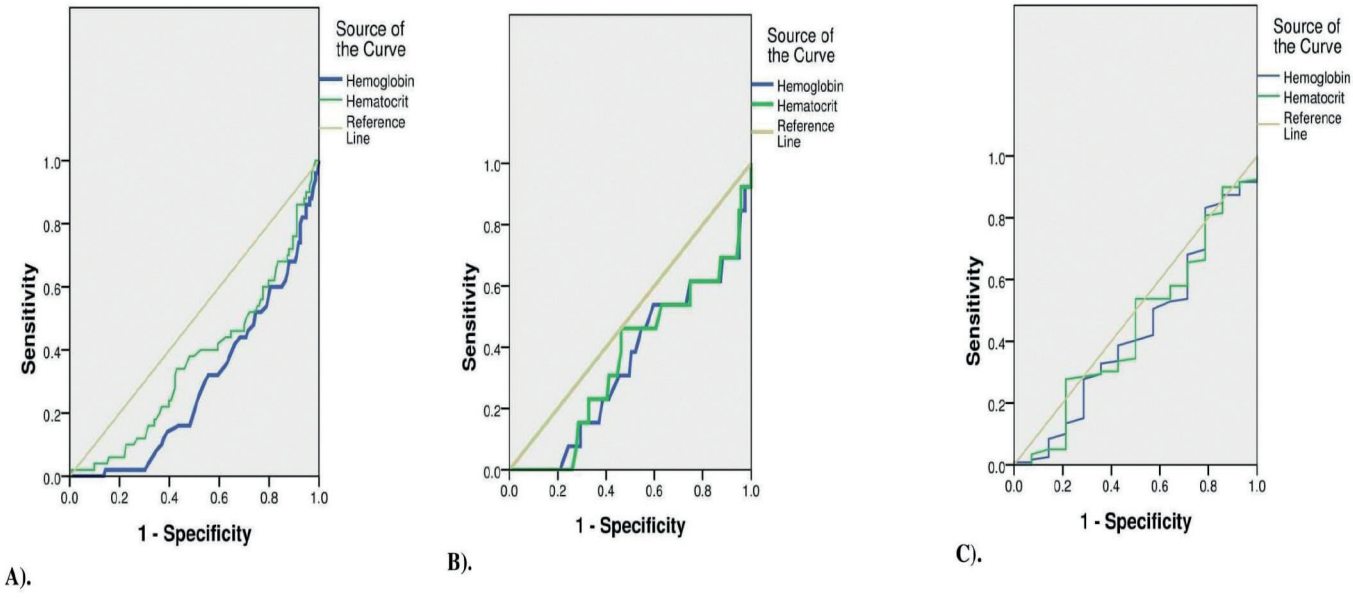

Figure 1: Receiver operating characteristic curve of the study A) case vs control, B) cardiac end point, and C) outcomes

atherogenic (23). Furthermore, in the iron-heart hypothesis revealed that the increase of iron as a result of elevated hemoglobin level also has the correlation with increase of LDL level (21). Iron participates in the generation (24) and or catalyzes the creation of powerful oxidant species. This leads to lipid modification, which is essential for atheroma formation (25).

Elevated hematocrit had been associated with several conditions including atherosclerosis, coronary artery disease, and myocardial infarction (26). In this study, we reported the association between hematocrit level and the risk of CHD. Our study showed that elevated hematocrit level was associated 2.17 fold with the risk of CHD [OR 95% CI=2.17 (1.11-4.25), p=0.024]. Several studies had reported the correlation between CHD and the risk of CHD in different population. We collected studies in Pubmed and EMBASE, totally there were seven studies evaluated the correlation between hematocrit level and the risk of CHD (Table 4). However, data were not compatible for a meta-analysis. Therefore, we compared our data narratively. Two retrospective studies conducted by Kunnas et al. in Finland and Zhong et al. in Europe population found that elevated level of hematocrit had a significant association with the risk of CHD (27,28). Furthermore, five cohort studies conducted in Japan (29,30), USA (31), and Puerto Rico (32) also found that hematocrit had a significant association with the risk of CHD. Overall, our result was consistent with some studies evaluating the correlation between hematocrit level and the risk of CHD. In addition, in Table 2, it was implied that the higher the hematocrit represented the higher the severity and the worse the prognosis. See Figure 1. However, we did not find that this trend had a significant correlation.

The theory regarding mechanism of hematocrit in CHD is limited. Hematocrit, the proportion of the total blood volume occupied by red blood cells, is a major determinant of blood viscosity and has an important role in regulating blood flow. Both increased and decreased hematocrit had been proven to be associated with the risk of CHD (30). However, because of our results, we only discussed regarding elevated hematocrit correlated with the risk of CHD. There are three plausible mechanisms regarding the correlation between hematocrit and CHD, 1) elevated hematocrit may translate into increased blood viscosity, peripheral resistance, and decreased cardiac output (33); 2) the effect of elevated hematocrit may correlate with other CHD risk factors such as hypertension (34); and 3) elevated hematocrit may lead to atherosclerosis through red blood cells aggregation (31). In correlation with atherosclerosis, elevated hematocrit leads to increase adhesiveness of platelets by erythrocyte-derived ADP. This causes dispersion of platelets in the subendothelial surface, which is the beginning of atherosclerosis (30).

This result indicated that hemoglobin and hematocrit levels had a correlation with the risk of CHD. However, these results were not adequate to provide recommendations on the use of hemoglobin and hematocrit to evaluate CHD patients. Nevertheless, the results of all studies evaluating associations between hemoglobin and hematocrit levels with the risk of CHD worldwide showed that there is a significant association between hemoglobin and hematocrit with the risk of CHD. Therefore, the Organization of Cardiology needs to review the use of hemoglobin and hematocrit in patients with CHD.

Study Limitations

There were several limitations in this study. First, several CHD risk factors including history of premature CHD, family history of CHD, physical inactivity, and smoking status were not included in the study. Second, data regarding the correlation between hemoglobin and hematocrit levels with the risk of CHD were not compatible for meta-analysis.

CONCLUSION

It can be concluded that in our population, hemoglobin and hematocrit were indicated to be correlated with the risk of CHD. Our results may contribute to develop better understanding of the correlation between hemoglobin and hematocrit with the risk of CHD. In addition, the study also showed that hemoglobin and hematocrit are remain valuable as an easy and widely available predictor of CHD.

Ethics Committee Approval: This study was approved by local ethical committee.

Informed Consent: Informed written consent was waived because the study was a retrospective data analysis.

Authorship Contributions

Surgical and Medical Practices: J.K.F., D.I.S., M.S.R., Concept: J.K.F., Design: J.K.F., Data Collection or Processing: J.K.F., D.I.S., Analysis or Interpretation: J.K.F., D.I.S., Literature Search: J.K.F., D.I.S., Writing: Jonny J.K.F., D.I.S., M.S.R.

Conflict of Interest: There is no conflict of interest.

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