Total Flight Hours and Other Factors Associated with Hyperuricemia in Civilian Pilots

Simplisius Cornelis Tisera; Amilya Agustina; Dewi Sumaryani Soemarko

BACKGROUND: In the aviation world, hyperuricemia can endanger flight safety through the risk of incapacitation, either associated with gout disease or associated with an increased risk of cardiovascular disease. This study aims to determine the prevalence of hyperuricemia in civil pilots in Indonesia and the identification of risk factors for hyperuricemia in civil pilots in Indonesia.

METHODS: The study used a cross-sectional method from the medical records of civil pilots at the Aviation Medical Center, Jakarta, who were examined on 1 November 2019 through 30 April 2020. Data collected from medical records included: laboratory data of uric acid, age, total flight hours, Body Mass Index (BMI), and alcohol consumption. Hyperuricemia is a plasma urate concentration > 420 μmol · L^{-1}(7 mg · dl^{-1}).

RESULTS: The research sample amounted to 5202 pilots; 18.4% had hyperuricemia. Pilots who have total flight hours ≥5000 have a reduced risk of hyperuricemia by 24% compared to pilots with total flight hours <5000. Obese and overweight pilots had a 2.98 times and 1.36 times, respectively, greater risk of hyperuricemia than pilots who had a normal BMI. Based on BMI criteria classification of WHO Asia Pacific, obese is ≥25 and overweight is 23–24.9. Furthermore, compared to pilots who did not consume alcohol, pilots who consumed alcohol had a 14.68 times greater risk of developing hyperuricemia.

CONCLUSION: The prevalence of hyperuricemia in civil pilots in Indonesia is 18.4%. Obesity, overweight, and alcohol consumption increase the risk of hyperuricemia in civil pilots in Indonesia.

KEYWORDS: aircrews, alcohol, body mass index, obese, overweight, uric acid.

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Hyperuricemia conditions can result from excess uric acid production, reduced uric acid excretion through the kidneys, or a combination of both. The prevalence of hyperuricemia in Indonesia is still unknown with certainty due to the limited data available. Hyperuricemia can occur in all populations, including the aviation population. Based on regulation number 238 of the Director General of Civil Aviation in Indonesia from 2018, uric acid is one of the requirement tests for civilian pilot medical certification.[16] Hyperuricemia is one of the health conditions that can endanger flight safety through the risk of incapacitation of pilots associated with gout disease or associated with an increased risk of cardiovascular disease. Gout disease can cause painful joints or renal stones. Serum uric acid concentrations have been shown to be useful as a prognostic marker of heart failure,[2] pulmonary thromboembolism,[17] and primary pulmonary hypertension.[14] Hyperuricemia can trigger vascular endothelial dysfunction (VED). VED is a chronic pathological condition during which the generation and bioavailability of nitric oxide (NO) gets decreased due to reduction in expression and activation of endothelial nitric oxide synthase (eNOS). Hyperuricemia has been noted to decrease the vascular generation of NO through eNOS inactivation. NO has been noted to possess vasodilatory, antiplatelet, antiproliferative, antiatherogenic, permeability-decreasing and anti-inflammatory properties. With this vascular endothelial dysfunction, various cardiovascular disorders such as atherosclerosis, hypertension, coronary artery disease, and heart failure can occur.[3] Several studies have stated that hyperuricemia

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is associated with a significantly increased risk of cardiovascular diseases such as atherosclerosis, coronary artery disease, hypertension, and heart failure.[1,3,9,21] A study conducted by Liu Jing et al. in China in 2009 mentioned 43 pilots had hyperuricemia (10.1%) out of 425 pilots undergoing medical examination.[11] The purpose of this study is to determine the prevalence of hyperuricemia in civil pilots in Indonesia and the identification of risk factors for hyperuricemia in civil pilots in Indonesia. The hypothesis is that there is an association between total flight hours and hyperuricemia in civil pilots in Indonesia.

METHODS

Subjects

This study used a cross-sectional method. Data was taken from the medical records of civil pilots at the Aviation Medical Center, Jakarta, who were examined from 1 November 2019–30 April 2020. Due to the data being taken from medical records, there was no need for informed consent from the research subjects. Data collected from medical records included: laboratory data of uric acid, age, total flight hours, Body Mass Index (BMI), and history of alcohol consumption. The independent variables consist of total flight hours, age, BMI, and alcohol consumption. Meanwhile, the dependent variable is hyperuricemia. Inclusion criteria were as follows: male pilots and complete medical records. The exclusion criteria were as follows: pilots with estimated glomerular filtration rate (eGFR) <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and pilots taking drugs that can inhibit uric acid excretion such as aspirin, furosemide, thiazide, levodopa, acetazolamide, pyrazinamide, and ethambutol.

Hyperuricemia is a plasma urate concentration of more than 420 $\mu mol \cdot L^{-1}$. Total flight hours were classified into two groups: 100–4999 h and 5000–33,100 h. The division of the categories was based on previous research (total flight hours associated with cardiovascular disease in civilian aircrew[4]). BMI classification is based on the WHO (World Health Organization) Asia Pacific criteria, in which obese is ≥25 and overweight is 23–24.9. History of alcohol consumption is divided into nondrinkers and drinkers.

Ethical clearance was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia. This study was undertaken after approval was granted by the Aviation Medical Center's Chief in Jakarta, Indonesia.

Procedure and Statistical Analysis

After data collection was done, Chi-squared analysis was performed on the comparison of the proportions of the variables of age, total flight hours, BMI, and alcohol consumption on hyperuricemia. From the results of this analysis, it can be ascertained whether there is an association between the independent variable and the dependent variable. Multivariate analysis (logistic regression) was also carried out to assess the association between several independent variables at once with the dependent variable. Statistical tests were interpreted using the alpha level of 0.05 for statistical significance. All data were processed using IBM® SPSS® Statistics Version 20.

Table I. Characteristics of Research Variables.

VARIABLE	SAMPLE *N* = 5205	%
Age		
<30 yr	2432	46.7
≥30 yr	2773	53.3
Total Flight Hours		
<5000	3160	60.7
≥5000	2045	39.3
Hyperuricemia		
No	4249	81.6
Yes	956	18.4
Body Mass Index (BMI)		
Normal	850	16.3
Underweight	59	1.1
Overweight	1047	20.1
Obesity	3249	62.4
Alcohol Consumption		
Non-Drinkers	5091	97.8
Drinkers	114	2.2

RESULTS

Samples obtained in this study were 5399 pilots. Of the 5399 pilots, 194 met the exclusion criteria, leaving 5205 pilots for this analysis. **Table I** presents the percent distributions or frequency of the variable in this study, including age, total flight hours, hyperuricemia, BMI, and alcohol consumption, among the 5205 pilots. The prevalence of hyperuricemia in civil pilots in Indonesia was 18.4%.

Table II demonstrates that pilots with obesity, overweight, and alcohol consumption were more likely to have hyperuricemia. As shown in **Table III** (final model), obese, overweight, and

Table II. The Association Between Age, Total Flight Hours, BMI, Alcohol Consumption, and Hyperuricemia.

	HYPERURICEMIA			
VARIABLE	YES (*N* = 956) *N* (%)	NO (*N* = 4249) *N* (%)	ODDS RATIO (MIN–MAX) (95% CI)	*P*
Age				
≥30 yr	456 (16.4%)	2317 (83.6%)	0.76 (0.66–0.88)	<0.001[CS]
<30 yr	500 (20.6%)	1932 (79.4%)	Reference	
Total Flight Hours				
≥5000	322 (15.7%)	1723 (84.3%)	0.75 (0.64–0.86)	<0.001[CS]
<5000	634 (20.1%)	2526 (79.9%)	Reference	
BMI				
Obesity	738 (22.7%)	2511 (77.3%)	2.75 (2.16–3.51)	<0.001[CS]
Overweight	131 (12.5%)	916 (87.5%)	1.34 (1.00–1.79)	0.049[CS]
Underweight	5 (8.5%)	54 (91.5%)	0.87 (0.34–2.23)	0.767[CS]
Normal	82 (9.6%)	768 (90.4%)	Reference	
Alcohol Consumption				
Drinkers	88 (77.2%)	26 (22.8%)	16.47 (10.57–25.66)	<0.001[CS]
Non-Drinkers	868 (17.0%)	4223 (83.0%)	Reference	

[CS]Chi-squared test.

Table III. Multivariate Analysis.

VARIABLE	ODDS RATIO ADJUSTED (MIN–MAX) (95% CI)	*P*
Age		
≥30 yr	0.75 (0.62–0.91)	0.004
<30 yr	Reference	
Total Flight Hours		
≥5000	0.76 (0.62–0.93)	0.007
<5000	Reference	
BMI		
Obesity	2.98 (2.33–3.83)	<0.001
Overweight	1.36 (1.01–1.83)	0.042
Underweight	0.86 (0.34–2.22)	0.760
Normal	Reference	
Alcohol Consumption		
Drinkers	14.68 (9.35–23.06)	<0.001
Non-Drinkers	Reference	

Nagelkerke $R^2 = 0.10$.

alcohol consumption were identified as the dominant risk factors associated with hyperuricemia in civil pilots. Specifically, obese and overweight pilots had a risk of 2.98 times [OR adjusted 2.98; 95% CI = 2.33–3.83; df = 1; $P < 0.001$] and 1.36 times [OR adjusted 1.36; 95% CI = 1.01–1.83; df = 1; $P = 0.042$], respectively, greater risk of hyperuricemia compared with pilots who had a normal BMI. Furthermore, compared to pilots who did not consume alcohol, pilots who consumed alcohol had a 14.68 times greater risk of developing hyperuricemia [OR adjusted 14.68; 95% CI = 9.35–23.06; df = 1; $P < 0.001$].

DISCUSSION

This study found that the prevalence of hyperuricemia was 18.4% in civilian pilots in Indonesia. This number is greater than the prevalence of pilots in China in 2009, which was 10.1%.[11] The high prevalence rate of hyperuricemia among civilian pilots in Indonesia also illustrates that several pilots in Indonesia have a risk of incapacitation, both associated with gout disease and associated with an increased risk of cardiovascular disease. Based on data from the Royal Air Force, United Kingdom, the prevalence of civilian pilots who die in airplane accidents due to coronary artery disease is 19%.[19] Also, one of the effects of hyperuricemia is the formation of kidney stones. In flight, sudden incapacitation due to renal colic pain is the main aeromedical problem associated with kidney stones. Nearly about 5–10% of patients with kidney stones are a type of uric acid stone.[6] A study reviewing the causes of incapacitation in pilots in the U.S. Air Force revealed there were three cases onboard flights over 10 yr caused by renal colic.[6]

The results of this study indicated that there was an association between total flight hours and hyperuricemia. Pilots who have total flight hours of ≥5000 have a reduced risk of hyperuricemia by 24% compared to pilots with total flight hours <5000. Total flight hours are related to hypoxia and the amount of cosmic radiation received by the flight crew. The hypoxia present in flight is hypobaric. Tissue hypoxia increases purine catabolism and leads to increased uric acid levels.[8] Meanwhile, cosmic radiation exposure is cumulative. The higher the total flight hours, the higher the cosmic rays.[7,13] Exposure to cosmic radiation can trigger free radical reactions and causes lipid peroxidation. Lipid peroxidation is a process in which free radicals remove electrons from lipids, producing reactive intermediates that can undergo further reaction. The end product of this reaction is 4-hydroxynonenal (4-HNE). Excessive production of 4-HNE might be sufficient to cause obesity,[7,13] which leads to increased uric acid levels. These theories differ from the results of this study because the physiological response in the human body to intermittent hypoxia and cosmic radiation varies. Also, the Nagelkerke R^2 value of 10% indicates that there is still 90% of the influence of variables or other factors outside of the currently studied variables. Many factors play a more significant role in influencing hyperuricemia, including food and beverage consumption patterns.

As with total flight hours, this study showed an association between age and hyperuricemia. Pilots ≥30 yr of age reduced the risk of hyperuricemia by 25% compared with pilots <30 yr of age. In theory, it is stated that one of the consequences of the aging process is a deficiency of the hypoxanthine phosphoribosyl transferase (HPRT) enzyme. This enzyme has a role in converting purines into purine nucleotides. If this enzyme is deficient, the purine in the body can increase. The xanthine oxidase enzyme will metabolize purines that cannot be metabolized by the HPRT enzyme into uric acid.[15] This theory is different from this study's results because pilots over the age of 30 may pay more attention to the type of food eaten than pilots who are less than 30 yr of age. Age is not the main factor that plays a role in changes in uric acid in the blood. Many other factors play a more significant role in the increase in uric acids, such as the habit of eating foods high in purines.

Meanwhile, in terms of BMI, pilots who were obese and overweight had 2.98 times and 1.36 times greater risk of experiencing hyperuricemia than pilots who had a normal BMI. According to the theory, this condition states that obesity can increase uric acid levels through two processes: excess uric acid production and decreased uric acid excretion.[12,18] Thus, BMI is one of the points that need to be considered in every pilot medical examination at the Aviation Health Center.

Furthermore, compared to pilots who did not consume alcohol, pilots who consumed alcohol had a 14.68 times greater risk of experiencing hyperuricemia. This study relies only on medical records that provide information on drinkers and non-drinkers. It is not known how often and how much alcohol a pilot consumes. The power of this risk factor might be low because of such a small number: only 114 drinkers out of 5205 pilots. A meta-analysis study conducted by Li et al. in 2017 stated that alcohol consumption was positively associated with hyperuricemia and gout.[10] Alcohol intake has been identified as an essential risk factor for hyperuricemia and gout. Ethanol consumption has been shown to increase uric acid production through ATP degradation/depletion. Besides, the byproduct of alcohol, namely lactic acid, inhibits uric acid excretion in the kidneys, increasing serum uric acid levels.[5,10,20]

As seen in Table III, the multivariate analysis shows the values of the odds ratio adjusted for total flight hours ≥5000 and age ≥30 are below 1. This indicates that they were protective factors for hyperuricemia. Meanwhile, pilots with obesity, overweight, and alcohol consumption increase the risk of developing hyperuricemic conditions.

This study has limitations because it was carried out using only secondary data sourced from medical records data without direct data collection by interview or questionnaire. Variables obtained through filling out questionnaires, such as consumption of high-purine foods that affect serum uric acid concentrations, have not been implemented. However, this study took quite a lot of samples within 6 mo. This study was to look for the prevalence and risk factors for hyperuricemia in civilian pilots in Indonesia, which seems to be the first time this has been done in Indonesia because the authors have not found a similar study.

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