Circulating albumin-to-fibrinogen ratio may be a risk indicator for venous thromboembolism: findings from a population-based prospective cohort study

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Key words: Albumin; Fibrinogen; Albumin-to-fibrinogen ratio; Venous thromboembolism; Cohort study.

Contributions: SKK: Study design, data analysis and interpretation, drafting manuscript, and revising manuscript content and approving final version of manuscript; SK: Study design and and revising manuscript content and approving final version of manuscript; AV: Study design and revising manuscript content and approving final version of manuscript; JAL: Study design and conduct, responsibility for the patients and data collection, and revising manuscript content and approving final version of manuscript.

Conflict of interest: The authors declare no potential conflict of interest.

Funding: Prof. Laukkanen acknowledges support from The Finnish Foundation for Cardiovascular Research, Helsinki, Finland.

Acknowledgements: The Authors thank the staff of the Kuopio Research Institute of Exercise Medicine and the Research Institute of Public Health and University of Eastern Finland, Kuopio, Finland for the data collection in the study.

Availability of data and material: There are no linked research data sets for this submission, because the authors do not have permission to share data.

Ethics approval: The research protocol was approved by the institutional review board of the University of Eastern Finland. All participants provided written informed consent.

Received for publication: 5 May 2022.
Accepted for publication: 1 June 2022.

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Licensee PAGEPress, Italy
Bleeding, Thrombosis and Vascular Biology 2022; 1:36
doi:10.4081/btvb.2022.36

ABSTRACT

Circulating albumin and fibrinogen levels, commonly considered as inflammatory markers, have been shown to be associated with venous thromboembolism (VTE) risk. Circulating albumin-to-fibrinogen ratio (AFR) has been proposed as a novel inflammatory biomarker, but its association with VTE risk has not been investigated. We aimed to assess the prospective association of AFR with VTE risk. Circulating albumin and fibrinogen levels were measured at baseline in 2,284 men aged 42-61 years. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated. During a median follow-up of 27.0 years, 156 VTE cases were recorded. In analysis adjusted for established risk factors, the HR (95% CI) for VTE comparing extreme tertiles of AFR was 1.53 (1.02-2.32), which remained similar on further adjustment for prevalent cancer, 1.52 (1.01-2.30). The associations of circulating albumin or fibrinogen with VTE risk were modest. Circulating AFR may be a stronger risk indicator for VTE compared with albumin or fibrinogen alone.

INTRODUCTION

Venous thromboembolism (VTE) which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease (CVD).[1] Apart from being a leading and preventable cause of deaths, VTE is associated with substantial disability and economic costs.[2] Major risk factors implicated in VTE development include immobilisation, trauma, surgery, cancer, hormonal therapy, obesity, and hypercoagulation disorders;[3] however, it has been reported that its causes are unknown in 25-50% of cases.[4] Identifying putative risk factors that could be valuable in the development of more effective preventive strategies is essential. In addition to alterations in the coagulation cascade, abnormalities in fibrin clot properties, endothelial dysfunction, dyslipidemia and hypercoagulable states, an inflammatory hypothesis has been postulated in the pathophysiology of VTE.[5] Indeed, circulating inflammatory markers have been shown to be associated with the risk

of VTE.[6] Circulating albumin and fibrinogen, commonly used markers for evaluating inflammatory conditions, have also been shown to be associated with the risk of VTE.[7,8] It has been reported that the addition of these markers to existing VTE risk assessment models could be used to improve risk discrimination and reclassification.[9,10] Circulating albumin-to-fibrinogen (AFR), a novel biomarker estimated from measurements of albumin and fibrinogen, is potentially useful for evaluating and monitoring inflammatory conditions.[11] Given that circulating AFR reflects the activity of both albumin and fibrinogen in combination, we hypothesized that AFR may be a more reliable risk indicator for inflammatory conditions compared to albumin or fibrinogen alone. The association between AFR and VTE has not been previously investigated. Using a population-based cohort of 2284 Caucasian men with no previous history of VTE, we aimed to assess the prospective association of AFR with VTE risk and evaluate separate associations of albumin or fibrinogen with VTE risk.

MATERIALS AND METHODS

Reporting of the study conformed to broad EQUATOR guidelines,[12] and was conducted according to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (Supplementary Files). This analysis employed the Kuopio Ischemic Heart Disease (KIHD) risk factor study, a general population-based prospective cohort study comprising men aged 42-61 years who were recruited from Kuopio and its surroundings in eastern Finland. The KIHD cohort was originally designed to investigate risk factors for atherosclerotic CVD in middle-aged and older men, given the high prevalence and incidence of coronary heart disease in this population group.[13] The research protocol was approved by the institutional review board of the University of Eastern Finland and all study procedures were conducted according to the Declaration of Helsinki. Details of the study design, recruitment methods and assessment of risk markers have been reported previously.[6] The baseline cohort comprised 2682 men who had baseline assessments performed between March 1984 and December 1989. In the current analysis, complete information on serum AFR, relevant covariates, and VTE outcomes was available for 2284 men. Serum albumin concentrations were measured using Coulter's bromcresol purple (BCP) colorimetric assay (Kone Specific, Kone Corporation, Espoo, Finland).[7,14] Plasma fibrinogen concentrations were determined in fresh plasma samples with excess thrombin using the Coagulometer KC4 device (Heinrich Amelung GmbH, Lemgo, Germany). We included all first VTE events that occurred from study entry through to 2018. These were identified by computer linkage to the National Hospital Discharge Registry data and a comprehensive review of available hospital records. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard models. All statistical analyses were conducted using Stata version MP16 (Stata Corp, College Station, Texas).

RESULTS

The mean [standard deviation (SD)] for age, AFR and circulating albumin levels of the 2284 men at baseline was 53 (5) years, 14.5 (3.0) and 42.3 (3.5) g/l, respectively. The median (interquartile range, IQR) for plasma fibrinogen was 2.96 (2.63-3.33) g/l (Table 1). Significant weak and inverse correlations were observed between AFR and age, alcohol consumption, SES, body mass index, total cholesterol, and triglycerides, whereas a significant weak and positive correlation was observed with high-density lipoprotein cholesterol. Values of AFR were significantly lower in men who smoked compared with non-smokers and those with histories of type 2 diabetes or coronary heart disease compared with those without these comorbidities (Table 1).

During a median (IQR) follow-up of 27.0 (17.2-31.0) years, a total of 156 VTE cases (annual rate 2.85/1000 person-years at risk; 95% CI: 2.44 to 3.34) were recorded. Comparing the bottom versus top thirds of AFR, the HR (95% CI) for VTE in analysis adjusted for age, systolic blood pressure, body mass index, total cholesterol, triglycerides, smoking status, history of type 2 diabetes, prevalent coronary heart disease, lipid medication, alcohol consumption, total physical activity, socioeconomic status, total energy intake, and history of cancer was 1.52 (1.01-2.30) (Figure 1). Analysis in the same set of participants showed no significant evidence of associations of albumin or fibrinogen with the risk of VTE (Table 1).

DISCUSSION

In this population-based prospective cohort involving middle-aged and older Caucasian men, baseline AFR was most weakly and inversely correlated with several risk markers for VTE. We observed a significant association between lower levels of circulating AFR and an increased risk of VTE. The association was independent of several established risk factors (such as age, body mass index, smoking status, history of type 2 diabetes, prevalent coronary heart disease, and history of cancer) and other potential confounders. Further evaluation in the same group of participants showed that AFR was a stronger risk indicator for VTE compared with circulating albumin or fibrinogen alone.

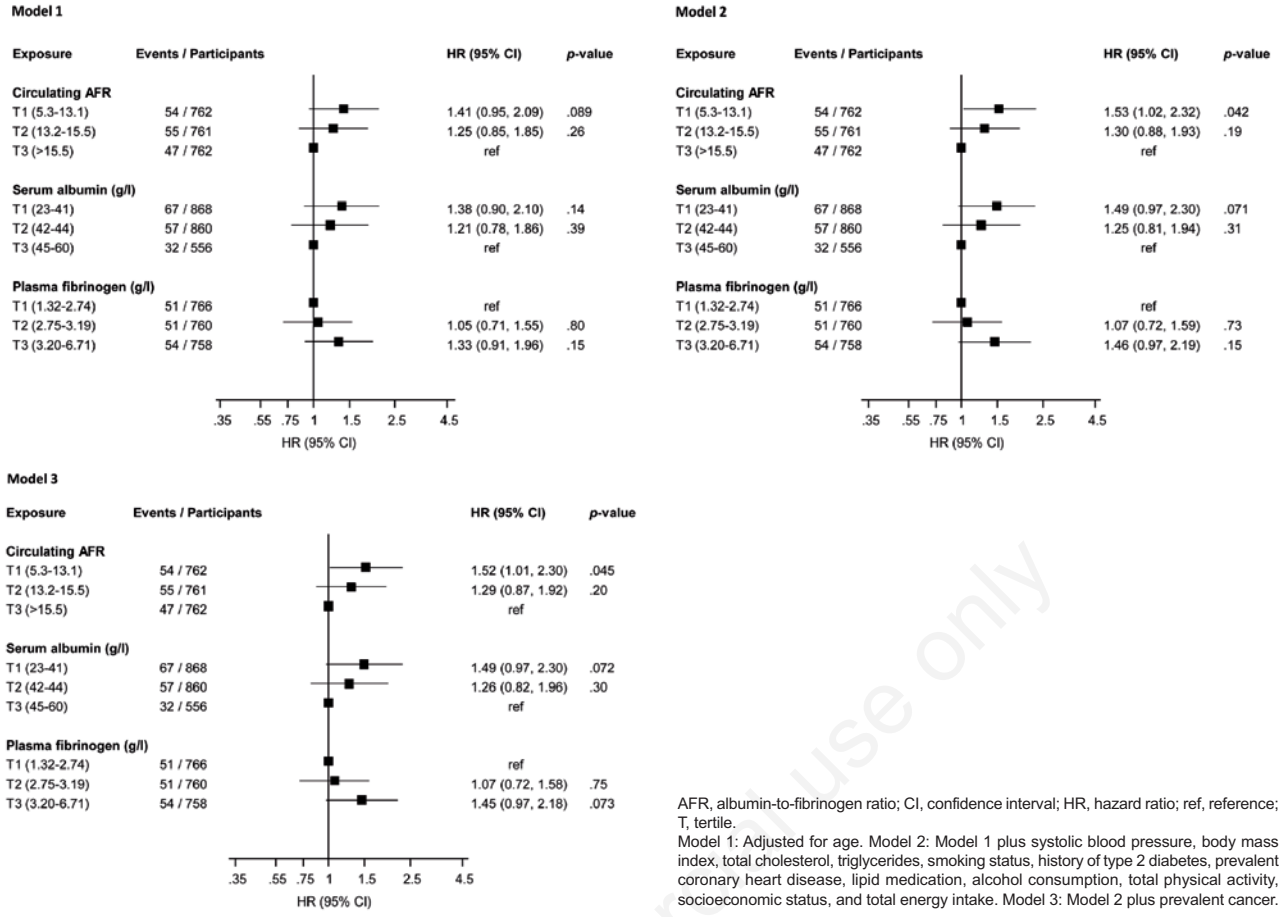
The current findings cannot be compared to any previous work given that this is the first evaluation of the prospective association between circulating AFR and VTE risk. However, a number of observational cohort studies have reported evidence of associations of low albumin and high fibrinogen levels with increased VTE risk.[7,8] Whereas serum albumin has been suggested to be causally related to VTE,[15] the relationship between circulating fibrinogen and VTE has not been demonstrated to be causal.[8] Possible factors underlying any association between low albumin and increased VTE risk may include inflammatory or hypercoagulable states,[16] underlying poor general health,[16] cancer, and atherosclerotic CVD,[17] which are all linked to the development of VTE.[5] Fibrinogen is a biomarker of chronic inflammation, has coagulative properties and is an important determinant of blood viscosity and platelet aggregation;[18] hence, elevated fibrinogen levels may increase the risk of thrombus formation.[19] The current findings suggest that circulating AFR may be a more useful risk indicator for VTE risk than albumin or fibrinogen alone and it can simply be estimated by dividing albumin measurements by that of fibrinogen. The potential clinical relevance of using AFR in VTE prevention and management deserves further evaluation.

The strengths of the current evaluation include the novelty, use of a large-scale population-based prospective cohort comprising a homogeneous sample of men

Table 1. Baseline characteristics of study participants and cross-sectional correlates of circulating albumin-to-fibrinogen ratio.

Characteristics	Mean (SD) or median (IQR)	Pearson correlation r (95% CI)[a]	Percentage difference (95% CI) in values of percentage of AFR per 1 SD higher or compared to reference category of correlate[b]
Albumin-to-fibrinogen ratio	14.5 (3.0)	-	-
Serum albumin, g/l	42.3 (3.5)	-	-
Plasma fibrinogen, g/l	2.96 (2.63-3.33)	-	-
Questionnaire/Prevalent conditions			
Age (years)	53 (5)	-0.15 (-0.19, -0.11)***	-0.47% (-0.60, -0.35)***
Alcohol consumption (g/week)	31.9 (6.4-91.9)	-0.11 (-0.15, -0.06)***	-0.33% (-0.46, -0.20)***
Socioeconomic status	8.42 (4.22)	-0.14 (-0.18, -0.10)***	-0.42% (-0.55, -0.30)***
Total energy intake (KJ/day)	9856 (2605)	0.01 (-0.03, 0.05)	0.03% (-0.10, 0.15)
Physical activity (KJ/day)	1215 (636-2005)		
History of type 2 diabetes (%)			
No	2196 (96.2)	-	ref
Yes	88 (3.9)	-	-0.86% (-1.50, -0.21)*
Current smoking (%)			
No	1588 (69.5)	-	ref
Yes	696 (30.5)	-	-1.83% (-2.09, -1.57)***
History of CHD (%)			
No	1724 (75.5)	-	ref
Yes	560 (24.5)	-	-0.71% (-1.01, -0.42)***
Lipid lowering medication (%)			
No	2272 (99.5)	-	ref
Yes	12 (0.5)	-	-1.29% (-2.99, 0.42)
Physical measurements			
BMI (kg/m^2)	26.9 (3.5)	-0.08 (-0.12, -0.04)**	-0.24% (-0.36, -0.11)**
SBP (mmHg)	134 (17)	0.02 (-0.03, 0.06)	0.05 (-0.08, 0.17)
DBP (mmHg)	89 (10)	0.01 (-0.03, 0.05)	0.04 (-0.09, 0.16)
Blood biomarkers			
Total cholesterol (mmol/l)	5.90 (1.07)	-0.13 (-0.17, -0.08)***	-0.38 (-0.50, -0.26)***
Triglycerides (mmol/l)	1.11 (0.81-1.58)	-0.04 (-0.08, -0.00)*	-0.13 (-0.25, -0.00)*
HDL-C (mmol/l)	1.29 (0.30)	0.11 (0.07, 0.15)***	0.32 (0.20, 0.44)***

*AFR, albumin-to-fibrinogen ratio; BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; ref, reference; SD, standard deviation; SBP, systolic blood pressure. [a]Pearson correlation coefficients between circulating AFR and the row variables; [b]Percentage change in values of circulating AFR per 1-SD increase in the row variable (or for categorical variables, the percentage difference in mean values of circulating AFR for the category versus the reference). Asterisks indicate the level of statistical significance: *p<0.05; **p<0.01; ***p<0.001.*



AFR, albumin-to-fibrinogen ratio; CI, confidence interval; HR, hazard ratio; ref, reference; T, tertile.
Model 1: Adjusted for age. Model 2: Model 1 plus systolic blood pressure, body mass index, total cholesterol, triglycerides, smoking status, history of type 2 diabetes, prevalent coronary heart disease, lipid medication, alcohol consumption, total physical activity, socioeconomic status, and total energy intake. Model 3: Model 2 plus prevalent cancer.

Figure 1. Associations of serum albumin-to-fibrinogen ratio, albumin, and fibrinogen with risk of venous thromboembolism.

who were nationally representative, the long-term follow-up of the cohort which was adequate for the ascertainment of VTE events, and adjustment for a comprehensive panel of VTE risk factors. The limitations included the inability to generalize the findings to women and other populations, lack of data on VTE subtypes, the relatively low VTE rate, and potential biases in observational cohort studies such as reverse causation, regression dilution bias, and inability to prove causation. Though we accounted for many potential confounders to ensure the validity of our associations, there is a potential for residual confounding due to errors in measured confounders and relevant unmeasured confounders such as medications like anticoagulants and antiplatelets. However, given we included an approximately general population sample with no history of VTE baseline, any participants that might be taking these medications will be a few. For example, only 12 men (0.5%) were on cholesterol-lowering medication. Furthermore, given that the present study is a post-hoc analysis of a prospective study that was designed to evaluate risk factors for atherosclerotic CVD, the current findings should be regarded as hypothesis generating. Further studies are needed to replicate these findings.

CONCLUSIONS

In middle-aged and older Caucasian men, circulating AFR appears to be a stronger risk indicator for VTE compared with albumin or fibrinogen levels alone.

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