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Platelet count is associated with cardiovascular disease, cancer and mortality: A population-based cohort study

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ABSTRACT

Introduction: Platelet count is used to determine bleeding risk and monitoring thrombopoiesis. While abnormal platelet counts are associated with mortality and morbidity, it is unclear whether it also apply to platelet counts within reference range. We investigated the relationship between platelet count ($100–450 \times 10^9$/L) and mortality, development of future cardiovascular disease (myocardial infarction, ischaemic stroke, or peripheral vascular disease), venous thromboembolism, bleeding or cancer in the general population.

Material and methods: We conducted a register-based cohort study of 21,252 adults (≥20 years) from the Danish General Suburban Population Study (GESUS). Laboratory results from GESUS were linked to information from national registers regarding morbidity and death. Cox proportional hazard regression was conducted with adjustment for age, sex, smoking status, haemoglobin, leukocyte count, C-reactive protein and Charlson comorbidity index.

Results: We found a U-shaped relationship between mortality and platelet count. Mortality was significantly increased for platelet count $<175 \times 10^9$/L or $>300 \times 10^9$/L. When categorizing platelet count using the interval $201–250 \times 10^9$/L as reference group, platelet count $301–450 \times 10^9$/L was associated with mortality, adjusted hazard ratio (HR) = 1.42(95% CI 1.06–1.90) and cardiovascular disease, adjusted HR = 1.32 (95% CI 1.03–1.69). Platelet count $100–200 \times 10^9$/L was associated with future cancer, adjusted HR = 1.28(95% CI 1.05–1.57), but not with future bleeding or venous thromboembolism.

Conclusions: Platelet count is associated with mortality, future cardiovascular disease, and future cancer.

1. Introduction

In clinical practice, the platelet count is frequently measured to assess bleeding risk and thrombopoiesis.

The inter-individual variation in platelet count is considerable [1,2], whereas the individual platelet count is very stable over time in healthy persons (low intra-individual variation) [3]. The tight regulation of platelet count proposes that platelets have non-haemostatic functions since a platelet count as low as $5–10 \times 10^9$/L is generally enough for maintaining vascular integrity and prevent spontaneous bleeding [4]. In agreement with this, mounting evidence describes a pertinent role for platelets in physiological processes such as immune response, angiogenesis and fibrosis formation [5–7]. Platelets may therefore independently affect morbidity and mortality and not just reflect an underlying disease. Abnormal platelet count is a marker of poor prognosis in some patient groups, e.g. in cancer [8–10] and in critically ill patients [11]. Further, platelet counts outside the reference range have been related to mortality among elderly and in the general population [12–14]. Recently, Tsai et al. found a U-shaped relationship between platelet count and mortality in elderly [15].

Platelet count has previously been related to cause-specific mortality, e.g. related to cancer and cardiovascular disease [15,16], but evidence concerning a relationship between platelet count and development of diseases in the general population is sparse.

The hypothesis of the present study was that persons from the general population with platelet count differing from the population median had increased mortality or risk of developing disease. The aim of the present study was to determine the relationship between platelet count ranging $100–450 \times 10^9$/L and mortality in the general population, and secondly to evaluate whether the platelet count was associated with development of future cardiovascular disease, venous thromboembolism, bleeding or cancer.

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2. Methods

2.1. Study population

The present study was a register-based cohort study of all participants in the Danish General Suburban Population Study (GESUS) [17]. In the GESUS study, all inhabitants in Naestved Municipality, Denmark, aged 30+ years as well as a random selection of the population aged 20–30 years were invited by mail [17]. The GESUS was conducted during December 2009–October 2013, comprised 21,362 persons and had an attendance rate on 43%.

2.2. Data source and clinical variables

Data were retrieved from the GESUS, the Civil Registration System in Denmark [18], and the Danish National Patient Register [19]. Identification of study subjects and linkage of relevant data was possible because Danish residents have a unique and permanent civil registration number permitting linkage between all Danish registries.

GESUS information retrieved was age, sex, smoking status, haemoglobin, leukocyte count, platelet count, mean platelet volume, C-reactive protein, and study participation date. Data regarding death or migration was available from the Civil Registration System. Data recorded in the Danish National Patient Register include dates of outpatient visits, hospital admission and discharge dates, and up to 20 diagnoses coded by physicians according to the World Health Organization's *International Classification of Diseases*, 8th revision (ICD-8), which covered 1977–1993, and the 10th revision (ICD-10) thereafter [20]. The Danish National Patient Register contains information on all discharges from public inpatient-hospital admissions since 1977 and on hospital outpatient specialist clinic visits since 1995. Denmark has very few private clinics all providing non-acute care. From the Danish National Patient Register information on current and previous diagnoses was retracted.

For each person, Charlson comorbidity index was calculated based on the diagnosis codes registered in the Danish National Patient Register during the 10 year period prior to participation in the GESUS (see Appendix A for diagnosis coding) [20]. We also used diagnosis codes from the Danish National Patient Register to retrieve information on defined health outcomes occurring after inclusion in the GESUS. Health outcomes comprised of cardiovascular disease, venous thromboembolism, bleeding or cancer. Cardiovascular disease was defined as myocardial infarction (ICD-10: I21, I22, I23), cerebrovascular disease (ICD-10: G45–46; I60–69), or peripheral vascular disease (ICD-10: I70–I74; I77) [20]. Other outcomes were cancer (ICD-10: C00–C85; C88; C90–C96) [20] and venous thromboembolism defined as deep venous thrombosis (ICD-10: I80.1–I80.3) or pulmonary embolism (ICD-10: I26). Bleeding was defined as haemorrhagic stroke (ICD-10: I61) [21] or gastrointestinal bleeding (ICD-10: K25.0–K25.2; K26.0–K26.2; K27.0–K27.2; K28.0–K28.2; K29.0; K92.0–K92.2) [22].

Included were persons with platelet counts within an a priori defined range of 100–450 $\times$ 10^9/L. We excluded patients with thrombocytopenia (platelet count < 100 $\times$ 10^9/L) or thrombocytosis (platelet count >450 $\times$ 10^9/L). The study was based on the assumption that platelet count is stable over time [3]. We evaluated whether persons had another platelet count measured ≥182 days after the date for participation in GESUS. If so, the change in platelet count was calculated. For investigation of development of a given disease, we excluded patients already diagnosed with the same disease before participation. The cohort was followed from participation date until emigration, end of follow-up (20 April 2015) or the occurrence of a study health outcome (death or disease), whichever occurred first. We determined the association between platelet count and outcome with the full dataset. Both results for the overall population and on subgroups based on sex are presented.

2.3. Ethics

The study was approved by the Danish Data Protection Agency (No. 2008-58-0035; No. 2015-331-1031). According to Danish law informed consent or review by an ethics board is not required for studies solely based on register data.

2.4. Statistics

Distribution of data was evaluated by Shapiro-Wilk and inspection of histograms. The relationship between platelet count and age or mean platelet volume was assessed using Spearman rho correlation's coefficient. The difference between platelet count in men and women was determined using Wilcoxon Rank sum test. The independent effect of platelet count on mortality or morbidity was studied in a Cox proportional hazard regression analysis controlling for age, sex, smoking status, haemoglobin, leukocyte count, C-reactive protein and Charlson comorbidity index. The assumption on proportional hazards was assessed graphically and found appropriate. Results were reported as Hazard ratios (HR) and 95% confidence intervals (95% CI). When evaluating the relationship between platelet count on a continuous scale and mortality, we performed cox proportional hazard regression with restricted cubic spline plot with three knots for the platelet count [23]. Nonlinearity of the curve was accepted if the *p*-value for coefficient of the second spline was <0.05 [24]. Further, the relationship between platelet count and outcomes were analysed with platelet count as a categorical variable and platelet counts within 201–250 $\times$ 10^9/L as reference group for Cox proportional hazard regression (15). Age, haemoglobin, leukocyte count and C-reactive protein were on a continuous scale. We used fractional polynomials to evaluate linearity assumption and for age, haemoglobin, and leukocyte count, cubic splines with three knots were derived and used in all analyses. Charlson comorbidity index were included as 0, 1, and ≥2. The categorical variables sex and smoking status (current smoker/non-smoker) were dichotomous. Missing values were omitted from analysis. For sensitivity analysis, we performed subgroup-analyses based on sex; age <65 years versus ≥65 years. In additional analysis, data were limited to persons without co-morbidities (Charlson co-morbidity index = 0) or persons with a normal C-reactive protein level (CRP ≤10 mg/L). Adjustments were unaltered. When relevant, analyses were repeated with the lowest platelet count group divided into two – 100–150 $\times$ 10^9/L and 151–200 $\times$ 10^9/L. Moreover, landmark analysis with landmark point at 120 days was performed. We evaluated the effect of excluding persons diagnosed with hepatitis, myeloproliferative disease or immune thrombocytopenia because these diagnoses could affect the platelet count. Finally, we investigated the correlation between mean platelet volume and the platelet count and evaluated whether adjustment for mean platelet volume changed the results.

Statistical analyses were performed using Stata software package (Stata 14.0, StatCorp, College Station, Texas, USA).

3. Results

We identified 21,252 (99.5%) GESUS participants with platelet count measurements. Excluded were 38 (0.2%) persons with thrombocytopenia of whom 24 (63%) were male sex, and 108 (0.5%) persons with thrombocytosis of whom 84 (39%) were male sex. For the study population, the mean follow-up time was 3.5 ± 1.1 years during which 443 persons died (2%). The study population characteristics are shown in Table 1. The mean change in platelet count was −7 x10^9/L ± 54 among persons (n = 7757) who had another platelet count obtained within the study period, but ≥182 days after participation in GESUS.

The median platelet count was 246 $\times$ 10^9/L (2.5th–97.5th percentile 155–381 $\times$ 10^9/L). Platelet count was higher among women, 260 $\times$ 10^9/L (2.5th–97.5th percentile 168–396 $\times$ 10^9/L, than men, 230 $\times$ 10^9/L (2.5th–97.5th percentile 146–356 $\times$ 10^9/L, p < 0.001. The median