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Immature platelet fraction and the extent of coronary artery disease: A single centre study

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ABSTRACT

Background and aims: Immature platelet fraction (IPF) represents the quote of younger and larger sized circulating platelets, a potential marker of platelet reactivity and major cardiovascular events. We aimed to assess the relationship between IPF levels and the prevalence and extent of coronary artery disease (CAD) in patients undergoing coronary angiography.

Methods: A cohort of consecutive patients undergoing coronary angiography in a single centre were included. Significant CAD was defined as at least 1 vessel stenosis >50%, while severe CAD was defined as left main and/or three-vessel disease. IPF levels were measured at admission by routine blood cells count (A Sysmex XE-2100).

Results: We included 1789 patients, divided according to quartiles values of IPF. IPF levels were directly related to active smoke ($p = 0.02$), and non-acute coronary syndrome as indication to angiography ($p < 0.001$), higher levels of haemoglobin and uric acid ($p < 0.001$, respectively) and lower platelet count ($p = 0.003$). Angiographic features did not significantly differ according to quartiles values of IPF, but for a lower degree of TIMI flow in patients with a higher percentage of reticulated platelets ($p = 0.01$) and a higher rate of lesions involving bifurcations ($p = 0.05$). IPF levels did not affect the prevalence of CAD (77% *vs.* 82.2% *vs.* 79.1% *vs.* 75.6%, $p = 0.34$, adjusted OR [95% CI] = 0.93 [0.82–1.05], $p = 0.22$), nor of severe left main/three-vessel CAD (28.5% *vs.* 34.4% *vs.* 32.2% *vs.* 33.1%, $p = 0.27$; adjusted OR [95% CI] = 0.99 [0.90–1.1], $p = 0.88$).

Conclusions: The present study shows that among patients undergoing coronary angiography, the immature platelet fraction (IPF) is not associated with the prevalence and extent of coronary artery disease, and, therefore, should not be overlooked as a marker of coronary atherosclerosis.

1. Introduction

Coronary artery disease (CAD) still represents the leading cause of mortality worldwide [1], despite the improvements in the management of patients with acute myocardial infarction and the efforts being accomplished to spread preventive measures in the general population [2–5]. In fact, the diagnosis of CAD is generally accomplished after a first acute cardiovascular event [6], therefore, raising the attention towards the identification of those early markers of atherosclerosis that could allow a better stratification of cardiovascular risk [7–9].

In particular, platelets represent a key player in the pathogenesis of CAD, being involved in endothelial dysfunction, the development of atherosclerotic lesions and its thrombotic complications [10]. Growing attention has been recently addressed to reticulated platelets, the fraction of younger platelets lastly released from the bone marrow, that have been suggested to display a greater aggregating potential, in view of their larger size and protein synthesis capability [11,12]. Immature platelets fraction (IPF) is a

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parameter similarly addressing the turnover of circulating platelets that displays a good correlation with the rate of reticulated platelets, but allows a more reproducible, cheaper and precise measurement [13,14]. However, contrasting data has been reported so far on the association of IPF with ischemic cardiovascular events and platelet reactivity [15–17], with no study specifically addressing the angiographic identification of coronary atherosclerosis. Therefore, we aimed at assessing the impact of IPF levels on the prevalence and extent of CAD in a cohort of consecutive patients undergoing coronary angiography.

2. Materials and methods

Patients, undergoing coronary angiography between September 2012 and June 2016 at the Ospedale "Maggiore della Carità", Novara, Italy, were consecutively enrolled to participate in a cross-sectional study. The only required inclusion criterium was the signature of a written informed consent. The study was approved by our local Ethical Committee. All demographic and clinical data were prospectively recorded in a dedicated database. Hypertension was defined as systolic pressure >140 mmHg and/or diastolic pressure >90 mmHg or if the individual was taking antihypertensive medications. Diabetes mellitus was defined as previous diagnosis, specific treatment administration (oral drug or insulin), fasting glycaemia >126 mg/dL or HbA1c > 6.5%. Chronic renal failure was defined for history of renal failure or an admission glomerular filtration rate (GFR) < 60 mol/min/1.73 m^2 by MDRD (Modification of Diet in renal Disease) formula.

2.1. Biochemical measurements

Blood samples were drawn at admission, in elective patients, a fasting period of 12 h was required. Glucose, creatinine, glycosylated haemoglobin and lipid profile were determined by standard methods [18]. Blood cells count was performed in a blood sample collected in tripotassium EDTA (7.2 mg) tubes and analyzed within 2 h from drawing by an automatic blood cells counter (A Sysmex XE-2100). The percentage of reticulated platelets was defined as the percentage of immature platelets within the total platelet count or immature platelet fraction (IPF), determined by a fully automated sorting system (forward light scatter versus fluorescence scatterplot) of the Sysmex XE-2100 instrument, as previously described [17]. The expected Coefficient of Variation (CV) was ≤20% according to the manufacturer.

2.2. Coronary angiography

Coronary angiography was routinely performed by a Siemens AXIOM ARTIS *d*TC instrument (Erlangen, Germany), with a preferential transradial access, by the Judkins technique, using 6-French right and left heart catheters. Quantitative parameters for coronary lesions were derived by an off-line analysis with an automatic edge-detection system for Quantitative Coronary Angiography (Siemens Acom Quantcor QCA, Erlangen, Germany). Minimal luminal diameter, reference diameter, percent diameter stenosis, and length of the lesion were measured. Significant CAD was defined as the presence of at least 1 coronary stenosis more than 50%. Severe CAD was defined as the presence of three-vessel and/or left main disease. In case of patients who had previously undergone percutaneous coronary interventions, the treated lesion was considered in the count of significantly diseased vessels. In carriers of coronary bypass grafts, native arteries and grafts were included in the evaluation of extension of coronary artery disease (number of diseased vessels).

2.3. Statistical analysis

Statistical analysis was performed using SPSS 22.0 statistical package. Categorical data were provided as percentage, whereas continuous data were expressed as mean ± SD. Analysis of variance and the Chi-square test were performed for continuous and categorical variables, respectively. Patients were grouped according to quartiles values of IPF. Multiple logistic regression analysis was used to evaluate the relationship between the percentage of reticulated platelets and CAD, after correction for baseline confounding factors (all variables displaying a significant association with IPF at univariate analysis (p value < 0.05) that were entered in the model in block. A p value ≤ 0.05 was considered statistically significant.

3. Results

We included in our study a total of 1789 patients, who were divided according to quartiles values of IPF (<1.8; 1.8–2.89; 2.9–4.39; ≥4.4%).

Table 1 displays the main clinical and demographic features of the study population. As shown, the rate of active smokers was significantly higher in patients with higher reticulated platelets ($p = 0.02$), as much as the rate of patients undergoing coronary angiography for a non-acute coronary syndrome indication ($p < 0.001$). We observed a direct relationship between IPF and higher levels of haemoglobin and uric acid ($p < 0.001$, respectively) and lower platelet count ($p = 0.003$).

Angiographic features did not significantly differ according to quartiles values of IPF, as shown in Table 2. but for a lower degree of TIMI flow in patients with higher percentage of reticulated platelets ($p = 0.01$) and a larger prevalence of lesions involving bifurcations ($p = 0.05$).

The prevalence of coronary artery disease did not significantly differ according to the levels of IPF (77% *vs.* 82.2% *vs.* 79.1% *vs.* 75.6%, p=0.34, OR [95% CI] = 0.95 [0.86–1.05], $p = 0.34$), as showed in Fig. 1.

Similar results were obtained when considering the prevalence of severe left main/three-vessel CAD (28.5% *vs.* 34.4% *vs.* 32.2% *vs.* 33.1%, $p = 0.27$; OR [95% CI] = 1.05 [0.96–1.15], $p = 0.27$), as shown in Fig. 2.

No impact of reticulated platelets (across quartiles) was confirmed after correction for baseline confounders both for CAD (adjusted OR [95% CI] = 0.93 [0.82–1.05], $p = 0.22$) and severe CAD (adjusted OR [95% CI] = 0.99 [0.90–1.1], $p = 0.88$).

4. Discussion

The present study represents the largest single centre cohort study attempting to define a role of immature platelet fraction on the prevalence and extent of coronary disease as detected at angiography. We found no impact of this platelet parameter on the rate of CAD or severe left main/three-vessel disease.

Recent advances in pharmacological therapies and percutaneous coronary interventions have dramatically improved the survival of patients with cardiovascular disease, especially after an acute myocardial infarction [19–22]. In particular, raising attention has been addressed to the crucial role of platelets in the pathogenesis of acute ischemic events, with emerging evidence in favour of a greater protection from acute thrombotic events with a more prolonged antiplatelet therapy [23,24].

Nevertheless, the preventive strategies developed so far have failed to reduce the burden of cardiovascular disease, with CAD still representing the leading cause of mortality worldwide. Therefore, efforts have been made to predict in advance the cardiovascular