Parameters of complete blood count do not predict on-treatment platelet reactivity in acute coronary syndrome patients

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Over the past ten years, a large body of evidence clearly demon-strated that acute coronary syndrome (ACS) patients with persistent high on-treatment platelet reactivity (HTPR) despite a well conduct-ed treatment with P2Y12 receptor antagonists are at higher risk for adverse cardiovascular events (ACVE) [1].Bothgeneticpolymor-phisms [2] and clinical variables [3] have been associated with HTPR, but all together these factors predict only a slight part of the observed variability in response to clopidogrel and other P2Y12-ADP receptor antagonists. Platelet function testing therefore remains the more accurate way to identify high risk patients with HTPR who may benefit from intensified antiplatelet regimen, even though ran-domized trials investigating the effect of antiplatelet regimen adjusted to the results of platelet function testing failed to demonstrate a clinical benefit yet. Nevertheless, platelet reactivity (PR) testing presents to date some limitations: it lacks of standardization, it requires specialized equipment and substantial blood sample volumes, and it is often costly and technically challenging.

Recently, parameters of complete blood count (CBC) which are widely available for routine clinical use, reproducible, inexpensive and non-invasive, have gained an increasing interest in the cardiovascular setting. The mean platelet volume (MPV) was indeed proposed as a marker of platelet activity, since larger platelets are haemostatically more active and thought to display a greater prothrombotic potential than smaller platelets [4]. Scarce studies investigating whether MPV might increase on-treatment PR found conflicting results [5,6,7,8], but meanwhile MPV was shown to predict outcomes in ACS patients in several studies [9].Otherwise, inflammation has been demonstrated to be significantly associated with high PR [10].New inflammatory markers derived from CBC as the platelet-lymphocyte ratio (PLR) and the neutrophil-lymphocyte ratio (NLR) could also potently be associated with PR since they were recently demonstrated to correlate with adverse cardiovascular outcomes in myocardial infarction patients [11], and unstable angina patients [12].

The aim of the present study was to investigate, in a large sample size cohort of ACS patients treated with P2Y12-ADP receptor antagonists, whether any of these CBC parameters could independently predict on-treatment PR assessed with the well established vasodilator stimulated phosphoprotein

platelet reactivity index (VASP-PRI). We retrospectively reviewed patients who underwent percutaneous coronary intervention (PCI) between January 2014 and August 2016 for the treatment of an ACS and were treated with dual antiplatelet therapy.

On admission and prior to the percutaneous coronary intervention (PCI), CBC, which included the total white blood cells, neutrophils, lymphocytes, platelets counts and MPV, were collected when available. All CBC were performed on an Advia 2120i haematology analyzer (Siemens, Saint-Denis, France). The PLR was calculated as the ratio of the platelet count to the lymphocyte count and the NLR was calculated as the ratio of the neutrophil count to the lymphocyte count. PR was assessed using the CY-QUANT VASP/P2Y12 enzyme-linked immunosorbent assay (Biocytex, Marseille, France) and the VASP-PRI calculated as previously described [13]. HTPR was defined as a VASP-PRI ≥ 50%. All statistical analyses were performed using the Graphpad Prism software v5.0 for windows (Graphpad Software Inc., San Diego, USA). Categorical data were expressed as counts (%) and compared using χ2 or Fisher's exact tests. Spearman's test was used to measure the strength of association between two variables. A receiver operating characteristic (ROC) curve analysis was performed to determine the optimum cut-off MPV, PLR and NLR values to predict HTPR. A two-tailed p value b 0.05 was considered significant.

Among patients that underwent PCI between January 2014 and August 2016, 565 patients had a pre procedural CBC and were further included in the analysis. Among these 565 patients, 426 (75.4%) were men and 139 (26.6%) were women. The median age was 65 years. One hundred twenty-four out of 565 patients (21.9%) presented a HTPR. Neither MPV, nor PLR, nor NLR were correlated with the VASP-PRI ($r = 0.029$, p = ns; $r = 0.025$, p=ns; $r = -0.35$, p = ns respectively; Fig. 1). ROC curve of MPV, PLR and NLR for predicting HTPR found areas under the curve close to 0.5 (0.528; 95%CI, 0.486–0.570 for MPV; 0.542; 95%CI, 0.500–0.584 for PLR; 0.516; 95%CI, 0.474–0.558 for NLR) representing a worthless test for predicting HTPR. The patients were further divided into quartiles based on MPV, PLR and NLR. Rates of patients with HTPR were determined in all the quartiles, and we found no difference in rates of patients with HTPR between quartiles of MPV, PLR or NLR for any of these CBC parameters (Table 1).

Previous studies targeting the role of MPV, PLR and NLR interestingly demonstrated that these markers reflect an increased inflammatory response and were predictive of long-term outcomes in patients with non-ST segment elevation myocardial infarction and ST elevation myocardial infarction [14]. Despite the obvious interest of such CBC parameters which presents the advantage to be automated, easy to perform, rapid, standardized reproducible, in-expensive and non invasive, our large sample size study provides evidence that neither MPV, nor PLR, nor NLR on admission can predict a HTPR under P2Y12-ADP receptors antagonists' treatment in ACS patients. Parameters of CBC should thus clearly not be considered as surrogate biomarkers of PR: even though inflammation plays an important role in HTPR, inflammatory markers are not predictors of HTPR but only factors contributing to HTPR, unable to replace platelet function testing.

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Fig. 1. Correlation between vasodilator stimulated phosphoprotein platelet reactivity index (VASP-PRI) and mean Platelet Volume (A), platelet-lymphocyte ratio (B) and neutrophil-lymphocyte ratio (C).

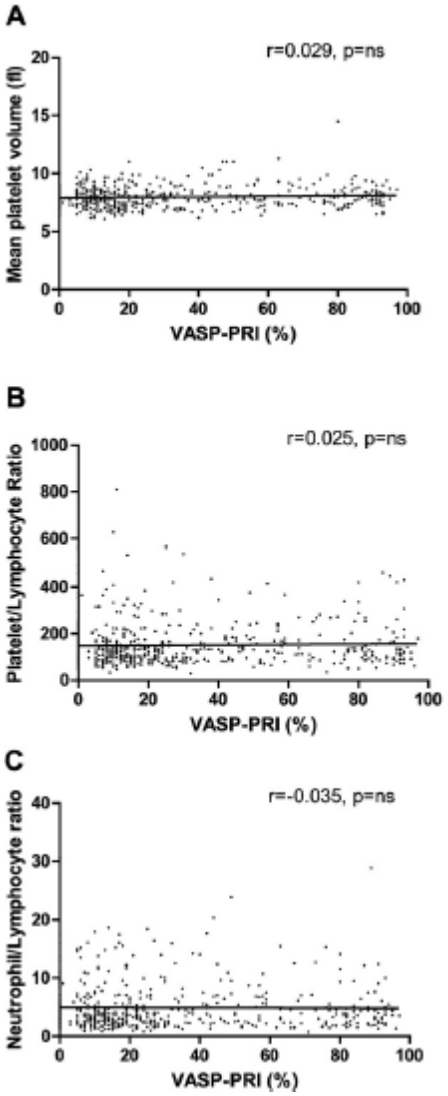

Table 1

Proportion of patients with high on-treatment platelet reactivity (HTPR) according to mean platelet volume, platelet-lymphocyte ratio and neutrophil-lymphocyte ratio quartiles.

		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P[a]
Mean platelet volume	HTPR, n(%)	27 (19.1)	34 (23.9)	27(19.1)	36(25.5)	0.2417
Platelet/lymphocyte ratio	HTPR, n(%)	26 (18.4)	32 (22.6)	29(20.8)	36(25.5)	0.2391
Neutrophil/lymphocyte ratio	HTPR, n(%)	38 (26.9)	26 (18.3)	32(22.6)	28(19.8)	0.5574