Abstract: P1500

Title: WHAT'S DRIVING RDW? IN-VITRO AND IN-SILICO EVIDENCE FOR OXIDATIVE STRESS

Abstract Type: Poster Presentation

Session Title: Iron metabolism, deficiency and overload

Background:

Red blood cell distribution width (RDW) is a biomarker associated with a variety of clinical outcomes. While anemia and subclinical inflammation have been posed as underlying pathophysiology, it is unclear what mechanisms underlie these associations.

Aims:

We aimed to unravel the mechanisms *in silico* by using a large clinical dataset and subsequently validate our findings *in vitro*.

Methods:

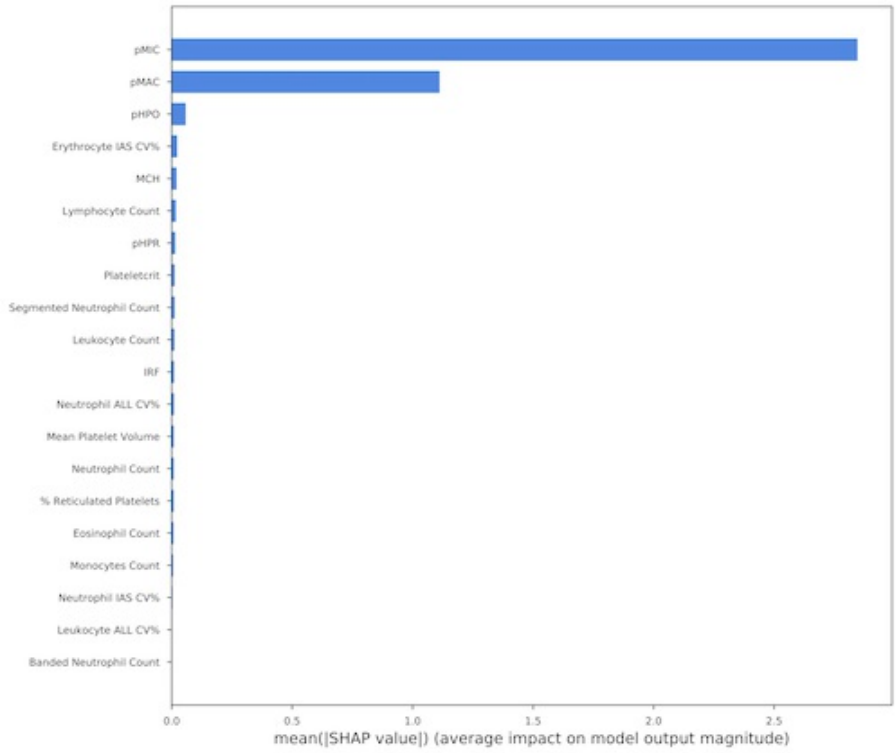
We retrieved complete blood counts (CBC) from 1,403,663 blood samples from the Utrecht Patient Oriented Database as measured on the Abbott CellDyn Sapphire, in order to model RDW by using gradient boosting regression (XGBoost) with different sets of predictors: one set with all variables (set 1), one set without percentage microcytic (pMIC) and macrocytic erythrocytes (pMAC) and mean corpuscular volume (MCV) (set 2), and one set without these variables and reticulocyte-related variables (set 3). We performed analyses in patients with and without anemia, in men and women, and in patients younger and older than 50. Additionally, we validated our model using data from the Abbott Allinity (n = 70) and data from the Abbott CellDyn Sapphire as measured in primary and secondary care (n = 513,564). We then validated our hypothesis regarding oxidative stress using an *in vitro* approach, where we induced blood samples with oxidative stress. Additionally, we measured erythrocyte deformability, by using Laser Optical Rotational Red Cell Analyzer techniques, and vesiculation.

Results:

Only pMIC and macrocytic pMAC erythrocytes and MCV were most important in modelling RDW (RMSE=0.40, R^2=0.96), considering removing the variables in sets 2 (RMSE=1.00, R^2=0.76) and 3 (RMSE=1.34, R^2=0.57) resulted in significantly worse performance. Subgroup analyses showed similar performance pattern, and validation in both Allinity data (RMSE=0.75, R^2=0.87) and primary and secondary care data (RMSE=0.45, R^2=0.94) confirmed the generalizability of the model as built on set 1. Our *In vitro* result after induction of oxidative stress underscored our results, as we observed an increased RDW and decreased erythrocyte volume, as well as increased pMIC, yet no vesiculation was observed. Furthermore, we found that deformability decreased as a result of oxidative stress possibly affecting sphericity of erythrocytes.

Summary/Conclusion:

We found that erythrocyte size, especially pMIC, is most informative in modelling RDW, but no role for anemia or chronic subclinical inflammation. Furthermore, oxidative stress may affect deformability of erythrocytes, and may therefore play a role in the association between RDW and clinical outcomes.



Keywords: Red blood cell, Erythrocyte, Machine learning