Reviewer’s report

Title: Peripheral blood gene expression signatures which reflect smoking and aspirin exposure are associated with cardiovascular events

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Reviewer: Robert Meller

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Review of "Peripheral blood gene expression signatures which reflect smoking and aspirin exposure are associated with cardiovascular events"

This study looks at blood RNA signatures of patients with cardiovascular disease. They looked at genes associated with aspirin and smoking. They measured ITGA2B levels in patients; a gene they previously showed to be increased in patients who use aspirin, and a 5 gene panel associated with smoking (sGES). They outline how smoking is associated with platelet dysfunction, and platelet dysfunction is associated with higher risk of MACE. They also contend that aspirin reduces platelet dysfunction and the smoking reduces this effect. Therefore, they were interested to determine the aspirin smoking interaction in patients with high cardiovascular adverse events.

Patients were from the PREDICT clinical trial (1581 patients, 3.5% had MACE). The authors show how elevated ITGA2B levels and the 5 Gene panel were associated with MACE. Unexpectedly, ITGA2AB was inversely associated with smoking gene panel score. Using logistic regression, they suggest combining ITG2AB and smoking gene panel scores were more accurate predictors of MACE that each alone.

Major- The majority of findings here are presented as overall summary of analysis, and two ROC curves. What is missing is the raw analysis of the data. For example they say that ITGA2B levels were inversely correlated with sGES but they do not show the data. It is had to assess the spread of their scores just based on summary tables. I would like to see the raw values for the genes that contribute to the sGES added to the supplementary data sheet.

While their previous study showed MACE and ITGA2B levels were independent, in this study higher levels of this aspirin response gene were associated with MACE. This was unexpected. The authors also did not observe the interaction between aspirin and smoking they expected. I respect the authors for discussing this in the discussion section, but as it stands I think that they are underplaying this in the study and the title. Especially since they report the addition of ITGA2 and sGES to be better indicators / predictors of MACE.
The patient population was an "at risk" population since they were referred for angiography. It was not clear how the levels of the aspirin response gene and sGES panel compare to their other studies (with respect to potential controls).

Minor

The authors use different statistical tests for determining the prediction power of their factors. It would be good to see a justification of why they changed their methods and did not stick with AUC. This will especially help a non-statistical expert understand their choices of tests.

Please define all abbreviations especially AIC

Please add R reference and any scripts/packages used in the analysis. Were any missing values imputed?

It was not clear what time frame the MACE endpoints occurred with respect to the time of the blood sample being taken.

The endpoints may be of different original/cause. Death, myocardial infarction and stroke or TIA. Was stroke stratified by ischemic vs. hemorrhagic stroke, and origin of ischemic clot???

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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