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Response to: Comment on 'Circulating cell-free miRNAs as biomarker for triple-negative breast cancer'

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Without a standardised method in the selection of diagnostic biomarkers, commonly seen in most of the preclinical studies, the use of statistical methods tends to vary between different groups based on the specific aims of the studies. Multivariate regression analysis is a rational way and not an uncommon methodology to evaluate the usefulness of miRNA signature as biomarkers, provided that the risk prediction of selected miRNAs has been taken into account. In one study, five miRNAs including up- and downregulated miRNAs were included in the panel of markers for prediction of recurrence and metastasis in prostate cancer (Nam *et al*, 2015). In a recent study on early detection of breast cancer, the authors compared the ROC analysis between individual miRNA and 3-miRNA signature (miR-199a, miR-29c and miR-424); the AUC of 3-miRNA signature was similar to that of miR-199a in terms of sensitivity and specificity (0.905 *vs* 0.883) (Zhang *et al*, 2015). If some of the selected miRNAs in the signature were associated with tumour stage while others not, it is likely that this may create a collinearity in the overall analysis of the miRNA signature (Xiong *et al*, 2014). In our case, however, even when miR-16 and miR-21 were differentially expressed between TNBC and non-TNBC, they are independent of tumour stage in the cohort, and combining the three miRNAs did not show a huge improvement, which was expected (Shin *et al*, 2015). Coherent with other studies, the miRNA panel did not necessarily yield a significant improvement on AUC as compared with single miRNA (Murray *et al*, 2015; Krishnan *et al*, 2015). Thus, improvement on biomarker analysis methodologies is awaited to tackle the heterogeneity in biomarker studies (Ray *et al*, 2010).

In lieu of a single marker, we believe a panel of signature would be a reliable representation for disease discrimination; a standardised analysis of data normalisation and also weighing of individual miRNA in the panel need to be considered. Using blood-based miRNA markers for diagnosis and prognosis will require validation in large-scale prospective and translational studies prior to clinical use.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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