Intensive Care Med (2016) 42:1824–1825
DOI 10.1007/s00134-016-4462-9

LETTER

Whole blood microRNAs as a prognostic classifier for acute respiratory distress syndrome 28-day mortality

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Dear Editor,

The acute respiratory distress syndrome (ARDS) is the leading cause of respiratory-related death disease in both intensive care unit (ICU) and hospital-wide, with a mortality rate of up to 40 % [1]. Despite a decreasing mortality rate of ARDS over time owing to improved management [2], this syndrome is underdiagnosed and insufficiently treated, and as a result remains highly deadly [1].

MicroRNAs (miRNAs) are small non-coding RNAs, usually approximately 22 nucleotides in length. They regulate gene expression by binding to specific target sites on messenger RNAs to either repress the translation of or degrade the transcript. MiRNAs play important roles in inflammation and infection [3], both of which are common manifestations in ARDS [4]. In addition, miRNAs are used to construct a prognostic classifier for early prediction of disease outcomes, including cancer [5].

Here we report a survival analysis as part of the Molecular Epidemiology Study of ARDS (MEARDS) from the ICU at Massachusetts General Hospital and Beth Israel Deaconess Medical Center. We collected 78 whole blood RNA samples from MEARDS. Expression of 754 human miRNAs identified by TaqMan OpenArray Human MicroRNA Panel was measured. After quality control screening (see electronic supplementary material, ESM), we selected 294 miRNAs for data analysis. Imputation was used to handle missing miRNA data (see ESM). We used multi-variate Cox proportional regression analysis to estimate the hazards ratio (HR) of miRNA for ARDS 28-day mortality. The Kaplan–Meier and log-rank method was performed to test the equality for survival distributions in different groups. All analyses were performed with R software (version 3.2.3) and Statistical Analysis System software (v.9.4, SAS Institute).

Demographic characteristics can be found in Table S1 in the ESM. We identified 19 miRNAs potentially associated with ARDS survival in patients with moderate to severe ARDS (Table S2 in ESM). Among them, five miRNAs were most differentially expressed, miR-628.3p (HR = 1.70, $p < 0.01$), miR-922 (HR = 1.05, $p < 0.01$), miR-505* (HR = 1.65, $p < 0.01$), miR-130b* (HR = 1.44, $p < 0.01$), and miR-624 (HR = 1.38, $p < 0.01$). In addition, on the basis of all statistically significant miRNAs, we used backwards elimination methods with Akaike information criterion to select miRNAs that have potential to predict ARDS 28-day mortality (miR-628.3p, miR-922, miR-766, miR-194, and miR-7). The final miRNA classifier was obtained by both most differential expression and backwards elimination. Expression of miRNA classifier larger than median was assigned as high expression, lower than median was assigned as low expression. The Kaplan–Meier curves for 28-day mortality groups, using the eight-miRNA classifier, are shown in Fig. 1. Time to death is shorter in patients with higher eight-miRNA classifier expression ($p = 0.04$), which is comparable to APACHE III (see ESM).

To our knowledge, this is the first study of miRNA as a prognostic classifier from whole blood for ARDS 28-day mortality. Whole blood contains both immune cell- and tissue-specific miRNAs and thus offers a major advantage for miRNA profiling compared with other tissue types. While our study confidence is limited by sample size and the mortality rate in this small cohort is high

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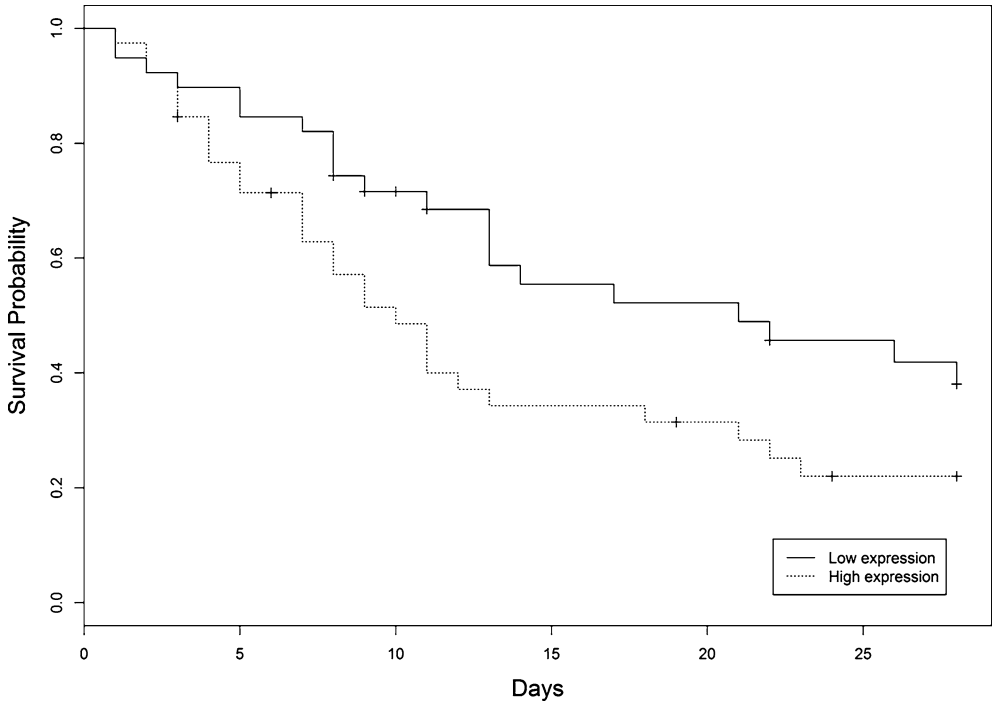

Fig. 1 Kaplan–Meier survival analysis according to the miRNA classifier grouped by expression level

and may not be representative of general ARDS cohort, the classifier containing miRNAs discovered in this study offers a potentially valuable, novel biomarker signature in clinical practice to better ARDS 28-day mortality prognosis.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-016-4462-9) contains supplementary material, which is available to authorized users.

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Acknowledgments
The authors thank Andrea Shafer and Sean Levy from Massachusetts General Hospital and Beth Israel Deaconess Medical Center for assistance in clinical data retrieval.

Compliance with ethical standards

Funding
This study was supported by Grants R01 HL060710 and P30 ES000002 (DCC) from the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health.

Conflicts of interest
The authors declare no competing interests.

Ethical standards
The institutional review boards of the Massachusetts General Hospital, Beth Israel Deaconess Medical Center, and Harvard T.H. Chan School of Public Health approved this study.

Accepted: 21 July 2016
Published online: 9 August 2016

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