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Epigenome-Wide Association Study for 28-day Survival of Acute Respiratory Distress Syndrome

Yichen Guo[1,2], **Ruyang Zhang**[1,3], **Zhaozhong Zhu**[1,4], **Sipeng Shen**[1,3], **Li Su**[1], and **David C. Christiani**[1,4,5]

[1]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA

[2]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA

[3]Department of Biostatistics, Ministry of Education Key Laboratory for Modern Toxicology, School of Public Health, Nanjing Medical University, Nanjing, China

[4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[5]Pulmonary and Critical Care Division, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Dear Editor

Acute respiratory distress syndrome (ARDS) is a severe lung disease with a mortality rate of over 40% among moderate-to-severe patients. A recent study demonstrated an association of microRNA (miRNA), an epigenetic regulator, with ARDS mortality [1]. Another epigenetic biomarker, DNA methylation, is associated with several inflammatory and pulmonary diseases [2]. DNA methylation, as a reversible epigenetic modification, offers potential diagnostic/prognostic and therapeutic value [2].

We conducted an epigenome-wide association study (EWAS) between DNA methylation and 28-day survival time in 185 moderate-to-severe ARDS patients from intensive care units (ICUs) (Table 1). DNA was extracted from whole blood, and methylation levels were measured on over 480,000 CpG sites. Associations between methylation and survival were evaluated by Cox models in two phases (discovery and validation) with adjustment for age, gender, APACHE III score and cell-type heterogeneity. Results were described as hazard ratio (HR) and 95% confidence interval (95% CI) per 0.01 unit increment of methylation beta values. Multiple testing corrections were performed using false discovery rate (FDR). Details are provided in the Supplementary Methods.

We identified four CpG sites that were significantly associated with ARDS survival in both discovery and validation phases (FDR<0.05) (Supplementary Table 1). Two sites are related to inflammation and infection, which are common manifestations in ARDS. Site

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval

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.

cg08504659 (discovery phase: HR=1.34, P=7.53×10^{-6}; validation phase: HR=1.22, P=1.58×10^{-4}) is located within *PTGDR* (encoding prostaglandin D2 receptor), which is a mediator of allergic inflammation and is recognized as a drug target of asthma [3]. Another site, cg04740513 (discovery phase: HR=0.97, P=1.23×10^{-5}; validation phase: HR=0.98, P=1.06×10^{-4}), is located within *ATP11A* (encoding integral membrane ATPase), which is associated with pulmonary disorders related to inflammation and fibrosis [4] and was recently identified as a novel element of the innate immune response and inflammatory response [5].

By integrating all four statistically significant methylation sites, we built a methylation risk score for each patient (Supplementary Methods). Patients with a higher methylation risk score had a significantly higher hazard of death within 28 days (HR=1.72 per 1 unit increment, P=2.73×10^{-7}); the mortality HR was comparable to that of APACHE III score (HR=1.71 per 40 unit increment, P=5.00×10^{-4}) (Supplementary Table 2). Similarly, the area under the receiver operating characteristic (ROC) curve (AUC) for prediction of 28-day ARDS mortality was comparable between methylation risk score (0.68) and APACHE III score (0.67) (Supplementary Figure 1).

We acknowledge some limitations of this study. First, although the two cohorts were recruited at different periods and measured separately (Supplementary Methods), all patients were recruited from two hospitals in the Boston area, which may limit generalizability. Second, all patients were moderate-to-severe cases recruited in the early years of our study, during a time in which high in-hospital mortality was common. However, our sensitivity analysis showed that the findings are consistent in sub-populations with lower mortality (Supplementary Methods, Supplementary Table 3).

To our knowledge, this is the first genome-wide epigenetic study among ARDS patients. While the sample size is limited, the discovered methylation sites showed putative biological importance, which highlights the feasibility of future large studies on DNA methylation in ARDS. In addition, the methylation risk score may ultimately be clinically useful for ARDS prognostic indication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline demographic characteristics of ARDS patients

N	92	93
Female, n (%)	21 (22.8)	44 (47.3)
Age, median years (range)	65 (22–87)	69 (22–97)
Baseline severity of illness (1st 24 hours of ICU admission)		
APACHE III, median (range)	83 (26–135)	96 (41–150)
PaO_2/FiO_2, median (range)	108 (34–193)	103 (37–200)
$100 \leq PaO_2/FiO_2 \leq 200$, n (%)	53 (57.6)	50 (53.8)
$PaO_2/FiO_2 < 100$, n (%)	39 (42.4)	43 (46.2)
Systolic blood pressure, <90 mmHg, n (%)	66 (71.7)	76 (81.7)
Heart rate, >100 beats/min, n (%)	70 (76.1)	73 (78.5)
Respiratory rate, >30 breaths/min, n (%)	50 (54.3)	40 (43.0)
Comorbidities		
Diabetes, n (%)	23 (25.0)	18 (19.4)
Predisposing conditions for ARDS		
Sepsis syndrome, n (%)	86 (93.5)	82 (88.2)
Septic shock, n (%)	77 (83.7)	77 (82.8)
Pneumonia, n (%)	25 (27.2)	35 (37.6)
Trauma, n (%)	1 (1.1)	1 (1.1)
Lung contusion, n (%)	2 (2.2)	1 (1.1)
Cancer		
Solid tumor, n (%)	3 (3.4)	5 (5.4)
Leukemia, n (%)	0	0
Non-Hodgkin's Lymphoma, n (%)	0	2 (2.2)
Survival Profiles		
28-day death, n (%)	60 (65.2)	85 (91.4)
Median survival days	14	10