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LETTER

Temporal trends of outcomes of neutropenic patients with ARDS enrolled in therapeutic clinical trials

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Dear Editor,

Outcomes of critically ill patients with neutropenia (including those with acute respiratory distress syndrome (ARDS)) improve over time, as suggested by data from observational studies [1, 2]. However, relevant data from randomized controlled trials are lacking. It is important to clarify the temporal trends of outcomes of patients with neutropenia as prognostic data like these provide important information for clinicians, patients and their family members when faced with decisions regarding intensive care unit (ICU) admission and supportive care.

We performed a secondary analysis of patient-level data from subjects with ARDS enrolled in six randomized controlled trials performed by the ARDS Network (ARDSNet), namely ARMA (published in 2000), ALVEOLI (2004), FACTT (2006), ALTA (2011), EDEN (2012), and SAILS (2014). Access to trial data was received after submission of our protocol (available upon request) and prespecified analyses, to the NIH/NHLBI BioLINCC. Our analysis was approved by the Weill Cornell Institutional Review Board (#1708018504). Some of our results were previously presented as a meeting abstract [3].

All enrolled patients had ARDS [4]. Neutropenia, determined on enrollment day 0, was defined as a total white blood cell count less than 1000 cells/μL [1, 2]. The primary outcome was 60-day mortality. Ventilator-free days and ICU-free days, as previously defined [4, 5], were secondary outcomes. Detailed statistical methods (including full model and adjustments) are provided in Supplementary Appendix.

Of 4333 subjects with ARDS enrolled in the trials, 204 (4.7%) had neutropenia. Detailed description of patients' characteristics and etiology of neutropenia is provided in Supplementary Tables 1 and 2. Enrollment of neutropenic subjects did not change over time ($p=0.28$). The median white blood cell count at enrollment was 277 [interquartile range (IQR) 137–600] cell/μL among neutropenic compared to 11,300 (IQR 7200–15,970) cell/μL among non-neutropenic patients. The unadjusted analysis is shown in the Fig. 1. After adjusting for variables previously shown to affect mortality of neutropenic patients (namely, age, baseline vasopressor requirement and renal dysfunction) [1], the odds of 60-day mortality decreased by an estimate 8% [95% confidence intervals (CI) − 0.8 to 16%, $p=0.073$] per year among neutropenic patients compared to 5.1% (95% CI 3.6–6.6%, $p<0.001$) per year among non-neutropenic patients. This adjusted difference between neutropenic and non-neutropenic patients was significant ($p<0.001$). Similarly, both ventilator-free days and ICU-free days increased more among neutropenic than non-neutropenic patients in the adjusted analysis ($p<0.001$ for both) (Supplementary Table 3).

By analyzing patient-level data from 4333 patients with ARDS enrolled in six rigorous ARDSNet trials, we found that clinically relevant outcomes, such as mortality, ventilator-free days and ICU-free days, of neutropenic patients improved significantly more over the course of two decades compared to outcomes of non-neutropenic patients. Although limited by a highly selected (e.g., exclusion of stem cell transplant subjects) and relatively small number of neutropenic patients as well as by consideration of center-dependent outcomes

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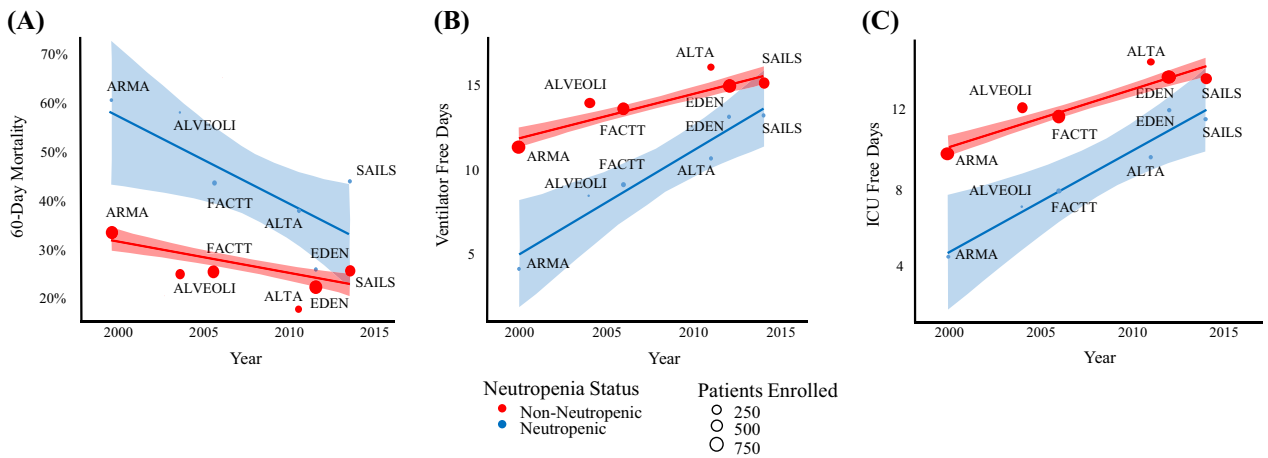

Fig. 1 Temporal trends of outcomes of patients with acute respiratory distress syndrome enrolled in therapeutic clinical trials. Temporal trends of **A** 60-day mortality, **B** ventilator-free days and **C** intensive care unit (ICU)-free days of neutropenic (blue) and non-neutropenic (red) patients with acute respiratory distress syndrome (ARDS) enrolled in six ARDSNet trials. Circles correspond to mean outcome (e.g., mean 60-day mortality) within each ARDSNet trial while circle size represents number of enrolled subjects, red and blue lines represent an unadjusted linear regression (95% confidence intervals) through the patient-level data points. Neutropenic patients per study: ARMA ($N=23$), ALVEOLI ($N=12$), FACTT ($N=57$), ALTA ($N=34$), EDEN ($N=42$), and SAILS ($N=36$)

(ventilator-free and ICU-free days), our findings are important. We show that the prognosis of these patients has improved over time even in prospective randomized controlled studies, whereas this trend has previously been observed only in retrospective observational studies [1, 6].

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-020-06263-4) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
AMKC is a cofounder, stock holder and serves on the Scientific Advisory Board for Proterris, which develops therapeutic uses for carbon monoxide (CO). AMKC also has a use patent on CO. AMKC served as a consultant for an advisory board meeting of Teva Pharmaceutical Industries, July 2018. None declared (DRP, KLH, ES, IIS).

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