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Economic disparities and survival from critical illness

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In the aftermath of the Ebola virus epidemic, a vivid lesson in geographical disparities emerged. When cared for in west Africa, an estimated 70·8% of patients with Ebola died.¹ By contrast, only 18·5% of patients managed in the USA or Europe died.² The most determinant factor in outcomes was a function neither of pathogen virulence nor of host susceptibility, but rather of geography.

The relevance of geography to understanding critical illness transcends epidemic outbreaks like Ebola. The 2016 update to the definition of sepsis³ was criticised for its uncertain applicability in low-income and middle-income countries. According to critics, Sepsis-3 was a definition written by and for North American and Western European intensivists,⁴ with insufficient consideration given to sepsis in much of the rest of the world.^{4,5} Similar concerns have been raised about acute respiratory distress syndrome (ARDS). In a study⁶ at a tertiary care hospital in Rwanda, investigators needed to re-define the disease (which has been termed the Kigali modification of the Berlin Criteria) to study the incidence and mortality of ARDS. In this population, mortality from ARDS was 50%—substantially higher than rates published in other ARDS epidemiological studies.

In *The Lancet Respiratory Medicine*, John G Laffey and colleagues provide us with the most comprehensive survey so far of global variation in ARDS.⁷ The investigators examined geographical variation in demographics, treatment patterns, and outcomes among 2813 patients with ARDS who received care in 459 intensive-care units in 50 countries. The investigators identified substantial variations across geographical regions, including increased use of neuromuscular blockade and prone positioning in patients with severe ARDS in high-income European countries compared with middle-income countries and non-European high-income countries, and higher risk-adjusted survival in European and non-European high-income countries than in middle-income countries.

Yet the authors' most salient finding was a strong association between country-level economic status and survival. For every additional US\$1000 increase in a country's gross domestic product (GDP) per person, the odds ratio for hospital mortality in patients with ARDS was 0·983. In view of the large range of GDPs among studied countries (\$1600–81

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000), this finding implies astonishing income-associated variation in ARDS survival. A patient admitted to hospital with ARDS in a representative high-income country (GDP per person \$38 000) has 0.59 times the odds of death compared with a similar patient admitted to hospital in a representative middle-income country (GDP per person \$6000).

The study provides few hints to explain this strong association between economic status and ARDS outcomes. By the coarse measurements available to the authors, the explanation was not simply resource availability, as nurse-to-bed or physician-to-bed ratios for intensive-care units differed little between middle-income countries and high-income countries. Major differences in severity of illness or underlying comorbidities also do not explain the geo-economic disparities. The authors identified geographical differences in management, including lower positive end-expiratory pressures and less frequent use of adjunctive measures such as neuromuscular blockade or prone positioning in middle-income countries. Yet these findings alone seem unlikely to explain the strong relationship between economic status and survival.

One hypothesis, untestable with the authors' available data, is that key unmeasured social factors influence the susceptibility and prognosis of patients with ARDS across socioeconomic and geographical strata. Although much has been published about the social determinants of health and chronic disease, less is known about their relative contributions to the outcomes of critical illness. Within US clinical trials, ARDS survival is lower among black and Hispanic patients than white patients, and this disparity is incompletely explained by illness severity.⁸ The effect of social factors on ARDS outcomes will need to be rigorously distinguished from other potential explanations for geographical variation, including differences in cause (infectious or otherwise) or variations in host genetic susceptibility. Laffey and colleagues' study emphasises the crucial need to untangle the

complex social, economic, demographic, genetic, and causative forces that interact to shape a given patient's disease course.

Irrespective of the mechanisms behind the association between economic status and ARDS survival, some implications are apparent. ARDS and sepsis are global diseases, necessitating a global perspective. In terms of both clinical investigations and development of disease definitions and practice guidelines, focus needs to extend beyond the patients and practitioners of western Europe, North America, and Australia. Intensivists from low-income and middle-income countries should be represented on the expert consensus panels that steer the field. When possible, clinical study of critical illnesses should not be restricted to the most resource-rich research environments. The social and economic context in which critical illnesses arise and critical care is delivered should be further interrogated as an understudied source of variation in outcomes.

In the past decade, a common lesson has emerged across the spectrum of pulmonary and critical care medicine, from the molecule to the population: diseases should be understood and studied within their environmental contexts. The malignant potential of a lung cancer cell is regulated by its tumour microenvironment,⁹ the virulence of a pneumonia pathogen depends on local ecological conditions within the respiratory tract,¹⁰ and the fibrotic potential of a lung epithelial cell is calibrated by its extracellular matrix.¹¹ Laffey and colleagues have shown vividly that to understand the presentation and prognosis of ARDS, it is essential to understand the social and economic context in which it arises.

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