7. Lalancette M, Carrier G, Laviolette M, Ferland S, Rodrique J, Bégin R, *et al.* Farmer's lung. Long-term outcome and lack of predictive value of bronchoalveolar lavage fibrosing factors. *Am Rev Respir Dis* 1993;148: 216–221.
8. Herrera J, Henke CA, Bitterman PB. Extracellular matrix as a driver of progressive fibrosis. *J Clin Invest* 2018;128:45–53.
9. Selman M, Pardo A, Barrera L, Estrada A, Watson SR, Wilson K, *et al.* Gene expression profiles distinguish idiopathic pulmonary fibrosis from hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2006;173: 188–198.
10. Furusawa H, Cardwell JH, Okamoto T, Walts AD, Konigsberg IR, Kurche JS, *et al.* Chronic hypersensitivity pneumonitis, an interstitial lung disease with distinct molecular signatures. *Am J Respir Crit Care Med* 2020;202:1430–1444.
11. Jung SM, Park K-S, Kim K-J. Integrative analysis of lung molecular signatures reveals key drivers of systemic sclerosis-associated interstitial lung disease. *Ann Rheum Dis* [online ahead of print] 2021 Aug 11; DOI: 10.1136/annrheumdis-2021-220493.
12. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, *et al.*; INBUILD Trial Investigators. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019;381:1718–1727.
13. Liu S, Chung MP, Ley B, French S, Elicker BM, Fiorentino DF, *et al.* Peripheral blood leucocyte telomere length is associated with progression of interstitial lung disease in systemic sclerosis. *Thorax* 2021;76:1186–1192.
14. Newton CA, Oldham JM, Ley B, Anand V, Adegunsoye A, Liu G, *et al.* Telomere length and genetic variant associations with interstitial lung disease progression and survival. *Eur Respir J* 2019;53: 1801641.
15. Lee JS, La J, Aziz S, Dobrinskikh E, Brownell R, Jones KD, *et al.* Molecular markers of telomere dysfunction and senescence are common findings in the usual interstitial pneumonia pattern of lung fibrosis. *Histopathology* 2021;79:67–76.
16. McDonough JE, Ahangari F, Li Q, Jain S, Verleden SE, Herazo-Maya J, *et al.* Transcriptional regulatory model of fibrosis progression in the human lung. *JCI Insight* 2019;4:e131597.

The Future of Outcome Prediction for Preterm Infants in the Neonatal ICU

Outcome prediction for prognosis or risk stratification is particularly important in the neonatal ICU as critically ill neonates are at high risk of mortality or long-term morbidity. There are several commonly used outcome prediction tools in neonatology. The majority of these tools use static measures such as data available at birth or within 24 hours of birth to predict the risk of subsequent mortality or neurodevelopmental impairment (1–3). Gestational age and birth weight are among the best predictor variables (4), such that clinical trials in preterm infants frequently use one or both of these variables for stratification to ensure balanced allocation. As early predictors do not take into account risk factors and complications that become apparent later during the hospitalization, tools incorporating respiratory support and selected postnatal morbidities were developed to better predict mortality, bronchopulmonary dysplasia, and neurodevelopmental impairment (5, 6). The use of prediction tools in neonatology to guide clinical decisions has not been tracked formally, and the impact on clinical care is unknown. A limitation of most of the currently available prediction models in neonatology is their reliance on data available at birth with limited or no sequential clinical and/or laboratory data.

In this issue of the *Journal*, Lavilla and colleagues (pp. 75–87) examined the discriminatory power of hourly changes in neonatal sequential organ failure assessment (nSOFA) scores from birth to predict death among 436 extremely preterm and extremely low-birth-weight infants. Hourly kinetics of the nSOFA score were strong predictors of mortality before discharge and within 24 hours after birth (7). The average score over the first 28 days was also associated with hospital mortality and major morbidities. Although mortality is rightly considered the most important outcome in neonatology, it is imperative to acknowledge that neurodevelopmental assessment at a later age was not addressed in the current prediction study. Neurodevelopmental impairment may be as important or more than some of the outcomes reported, including severe intraventricular hemorrhage, bronchopulmonary dysplasia, sepsis, necrotizing enterocolitis, and retinopathy of prematurity.

The nSOFA scoring system is based on the presence of mechanical ventilation and oxygen saturation as measured by pulse oximetry:F_{IO_2} ratio for respiratory dysfunction, presence of vasoactive medications and/or corticosteroids for cardiovascular dysfunction, and platelet count for hematologic dysfunction. These measures may be dependent on clinical practice. For example, the nSOFA scores may be artificially lower in a clinical setting where hypotension is managed more conservatively (8). Similarly, in centers with more use of mechanical ventilation rather than continuous positive airway pressure, use of lower rather than higher oxygen saturation targets (9), or avoidance of higher F_{IO_2} in favor of higher mean airway pressures, the model may not be as applicable. Thus, the generalizability of the results of this study may be limited and center-specific and may need to be validated externally.

The study by Lavilla and colleagues does not define if these are the best variables or weighting to predict the risk of adverse outcomes. It is possible that prediction might be improved using optimization of cutoff values or more granular continuous respiratory

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support data, additional vital signs measures, or more commonly collected laboratory values such as those available on standard blood gas analyzers. In the current study, the nSOFA score was calculated retrospectively. It needs to be determined if prospective nSOFA scores would improve clinical management decisions in neonatology. It is also important to note that although the nSOFA score is associated with poor outcomes, it does not follow that reducing the score by interventions would improve outcomes. The effect of artificially improving nSOFA scores by increasing platelet counts (10), limiting F_{IO_2} exposure in favor of increases in mean airway pressures, or avoiding vasoactive medications could have unintended consequences in sick neonates. It is also likely that measures of critical illness severity leading to changes in the nSOFA score such as the need for mechanical ventilation or vasoactive drugs are readily identified and perceived by clinicians caring for extremely preterm infants and hence may not alter a physician's intuitive assessment of prognosis (11).

Scoring systems need to be validated prospectively and in multiple settings before wider clinical use. The heart rate characteristics (HeRO) score that assesses measures of heart rate variability is an excellent example of a prediction system successfully tested from bench to bedside, including in a large multicenter randomized clinical trial (12) before its introduction into routine clinical care. A HeRO score that increases substantially above the baseline value or is high may indicate that the infant is developing sepsis. Clinicians provided with HeRO score data decreased the time to recognition and treatment of sepsis (12), which decreased the risk of mortality (13) in the randomized controlled trial. The HeRO score was associated with a lower risk of neurodevelopmental impairment compared with routine monitoring, likely because of early detection and treatment of sepsis (14). The authors reported recently that the HeRO score and nSOFA score provide complementary information on sepsis risk and sepsis-related mortality, with HeRO scores increasing before the blood culture, whereas the nSOFA scores increased at the time of culture (15).

However, the HeRO score relies on a single physiological value (heart rate variability), which may lead to low diagnostic accuracy in specific circumstances. For example, recuperating preterm infants taken off continuous positive airway pressure may develop increased episodes of bradycardia leading to an elevated HeRO score due to deescalation of respiratory support, whereas preterm infants with severe intraventricular hemorrhage may have a persistently elevated HeRO score. False negative results may occur among infants if the cause of deterioration is not due to sepsis, such as among infants with critical congenital heart disease. It is likely that future scoring systems that incorporate sequential physiological, laboratory, and clinical data may further improve the prediction or detection of infants at risk for death and major morbidities, including neurodevelopmental outcome. The advent of artificial intelligence into decision support tools, learning health systems, and evidence-based algorithms embedded into electronic medical records promises to improve prediction and real-time detection of infants at risk of adverse outcomes and inform clinicians so they can further improve the care of our most vulnerable infants. ■

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References

1. Ambalavanan N, Carlo WA, Bobashev G, Mathias E, Liu B, Poole K, *et al.*; National Institute of Child Health and Human Development Neonatal Research Network. Prediction of death for extremely low birth weight neonates. *Pediatrics* 2005;116:1367–1373.
2. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity–moving beyond gestational age. *N Engl J Med* 2008;358:1672–1681.
3. Parry G, Tucker J, Tarnow-Mordi W; UK Neonatal Staffing Study Collaborative Group. CRIB II: an update of the clinical risk index for babies score. *Lancet* 2003;361:1789–1791.
4. Salas AA, Carlo WA, Ambalavanan N, Nolen TL, Stoll BJ, Das A, *et al.*; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Gestational age and birthweight for risk assessment of neurodevelopmental impairment or death in extremely preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2016;101:F494–F501.
5. Ambalavanan N, Carlo WA, Tyson JE, Langer JC, Walsh MC, Parikh NA, *et al.*; Generic Database; Subcommittees of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Outcome trajectories in extremely preterm infants. *Pediatrics* 2012;130:e115–e125.
6. Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, *et al.*; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. *Am J Respir Crit Care Med* 2011;183:1715–1722.
7. Lavilla OC, Aziz KB, Lure AC, Gipson D, de la Cruz D, Wynn JL. Hourly kinetics of critical organ dysfunction in extremely preterm infants. *Am J Respir Crit Care Med* 2022;205:75–87.
8. Dempsey EM, Al Hazzani F, Barrington KJ. Permissive hypotension in the extremely low birthweight infant with signs of good perfusion. *Arch Dis Child Fetal Neonatal Ed* 2009;94:F241–F244.
9. Askie LM, Darlow BA, Finer N, Schmidt B, Stenson B, Tarnow-Mordi W, *et al.* for the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration. Association between oxygen saturation targeting and death or disability in extremely preterm infants in the neonatal oxygenation prospective meta-analysis collaboration. *JAMA* 2018;319:2190–2201.
10. Curley A, Stanworth SJ, Willoughby K, Fustolo-Gunnink SF, Venkatesh V, Hudson C, *et al.*; PlaNeT2 MATISSE Collaborators. Randomized trial of platelet-transfusion thresholds in neonates. *N Engl J Med* 2019; 380:242–251.
11. Meadow W, Pohlman A, Reynolds D, Rand L, Correia C, Christoph E, *et al.* Power and limitations of daily prognostications of death in the medical ICU for outcomes in the following 6 months. *Crit Care Med* 2014;42:2387–2392.
12. Fairchild KD, Schelonka RL, Kaufman DA, Carlo WA, Kattwinkel J, Porcelli PJ, *et al.* Septicemia mortality reduction in neonates in a heart rate characteristics monitoring trial. *Pediatr Res* 2013;74: 570–575.

13. Moorman JR, Carlo WA, Kattwinkel J, Schelonka RL, Porcelli PJ, Navarrete CT, *et al.* Mortality reduction by heart rate characteristic monitoring in very low birth weight neonates: a randomized trial. *J Pediatr* 2011;159:900–6.e1.
14. Schelonka RL, Carlo WA, Bauer CR, Peralta-Carcelen M, Phillips V, Helderman J, *et al.* Mortality and neurodevelopmental outcomes in the heart rate characteristics monitoring randomized controlled trial. *J Pediatr* 2020;219:48–53.
15. Zeigler AC, Ainsworth JE, Fairchild KD, Wynn JL, Sullivan BA. Sepsis and mortality prediction in very low birth weight infants: analysis of HeRO and nSOFA. *Am J Perinatol* [online ahead of print] May 2021; DOI: 10.1055/s-0041-1728829.

Reduced Aerobic Exercise Capacity in Adults Born at Very Low Birth Weight

No Small Matter!

Preterm birth (<37 wk) and low birth weight (LBW; <2,500 g) accounts for ∼11% and ∼15%, respectively, of all live births worldwide (1, 2). There is a growing concern for this population as those born preterm have an increased risk of early mortality from noncommunicable diseases (3) but, surprisingly, not morbidity at ages 18–43 years (4). There is also evidence for an association between birthweight and risk of mortality (5). Thus, there is an urgent need to determine the reason(s) for the increased risk of mortality in this ever-growing population. Aerobic exercise capacity is an important predictor of all-cause morbidity and mortality in, presumably, term-born, normal birthweight men (6) and women (7). However, this has not yet been established in those born preterm with very LBW (VLBW). Interestingly, there are multiple reports demonstrating reduced aerobic exercise capacity in adults born preterm (8), which raises the possibility that the lower aerobic exercise capacity may be the link between preterm birth and the increased mortality risk. Therefore, gaining a better understanding of the underlying cause(s) of reduced aerobic exercise capacity in adults born preterm with VLBW remains a clinically relevant endeavor.

In this issue of the *Journal*, Yang and colleagues (pp. 88–98) provide compelling evidence in a population-based cohort that impaired respiratory and cardiovascular function is associated with reduced aerobic exercise capacity in those born preterm with VLBW (9). A clinically reduced peak $\dot{V}O_2$, defined as <84% predicted, was found in 36% of VLBW adults compared with 17% of control subjects. Of those VLBW with a reduced peak $\dot{V}O_2$, 49% had bronchopulmonary dysplasia (BPD) compared with 32% with no BPD. Multiple regression models revealed that in addition to physical activity with body mass index, lung function and cardiac structure/function contributed equally to the differences in cardiopulmonary exercise testing outcomes between the VLBW and control groups. Remarkably, prematurity-related perinatal factors (e.g., BPD, antenatal steroids, small for gestational age, extreme prematurity) were not associated with the reduced aerobic exercise capacity in the VLBW group. Similarly, desaturation measured by delta Sp_{O_2} (peak exercise–baseline oxygen saturation difference measured by pulse oximetry) was not associated with reduced aerobic exercise capacity despite VLBW adults having a significantly reduced diffusing capacity for the lung for carbon monoxide and rate constant for carbon monoxide with normal V_A suggestive of pulmonary microvascular destruction/remodeling. These data support previous reports of normal pulmonary gas exchange in this population (8). This population-based study is an important advancement in the field by providing evidence for impaired lung structure and function and cardiac structure and function as equal contributors to impaired aerobic exercise capacity in adults born preterm with VLBW.

A limitation of the current study was that the authors were only able to quantify the *association* between impaired aerobic exercise capacity and the respiratory and cardiovascular physiology of adults born preterm with VLBW. Figure 1 provides a schematic representation of the relationship between altered heart and lung structure/function and exercise ability. Additional studies, particularly in large cohorts, are needed to determine whether a causative relationship exists between impaired cardiopulmonary function and reduced aerobic exercise capacity. For example, previous work in a small cohort has demonstrated that when adults born preterm breathe a helium–oxygen mixture (79% He, 21% O_2) during exercise, expiratory flow limitation, presumably caused by small airways (10), is reduced and exercise endurance is "normalized" relative to term-born control subjects (11). This example of a late life intervention supports the idea that aerobic exercise capacity and/or exercise endurance can be improved in adults born preterm when respiratory limitations are minimized. Likewise, in animal models of preterm birth, complicated by BPD, human umbilical cord–derived stem cells delivered into the airways to prevent abnormal lung development improved treadmill running distance to values similar to control animals, regardless of whether they were delivered before or after hyperoxia-induced alveolar injury (12). This example of an early life intervention in a preclinical model also supports the idea that exercise capacity could possibly be rescued in this population when the negative respiratory consequences of preterm birth are minimized or prevented.

Whether or not improving cardiac performance in adults born preterm with VLBW (i.e., a late life intervention) also

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