allele frequency in AA = 0.05). We confirmed this association, showing significance at *GREM2* lessened by two orders of magnitude ($P = 4.3 \times 10^{-4}$ to 1.2×10^{-2}) when comparing carriers of the *PVT1* risk haplotype to noncarriers. *GREM2* encodes Gremlin-2, an extracellular BMP antagonist in the same family as Gremlin-1, encoded by *GREM1*, a gene associated with SPF in EUs (5). *GREM2* is more highly expressed in the lung and blood of patients with idiopathic pulmonary fibrosis than in those of control subjects, and in fibrotic compared with nonfibrotic tissue, and elevated Gremlin-2 in human lung fibroblasts increases invasion and migration (10).

Although we acknowledge that our sample size was limited and that we do not have an AA replication cohort, our ability to replicate an effect that was previously identified in EUs within *TGFB3* (5) and to identify novel associations—including known expression quantitative trait loci in an AA-specific haplotype within *PVT1*—in the first WGS of pulmonary fibrosis in AAs highlights the need for and potential impact of research in this area. As in studies of EUs, we found associations implicating dysregulated TGF-β/BMP signaling, but with distinct genetic risk factors. Specifically, for AAs, the SPF risk haplotype in *PVT1* suggests an indirect effect on TGF-β signaling in addition to the effect seen at *TGFB3*, which encodes TGFβ-3, a cytokine involved in fibrosis and immune function (Figure 2). Likewise, our epistasis analysis suggests that SPF in EUs and AAs may uniquely inhibit antifibrotic BMP signaling through Gremlin-1 and Gremlin-2, respectively. Although dysregulation of the TGF-β/BMP signaling pathway may predispose patients to fibrosis, regardless of ancestry, the genetic influences on the mechanism of dysregulation appear to be ancestry specific and may mediate ancestry-related differences in prognosis. As both the first scan of SPF in a non-EU population and the first WGS of pulmonary fibrosis in a large cohort of AAs, our findings highlight the need for inclusion of underrepresented populations in research, as insights into mechanisms and potential treatments may otherwise remain undiscovered. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: We are grateful to the patients with sarcoidosis and control subjects who participated in this study. In addition, we express our gratitude to the research assistants, coordinators, and physicians who helped recruit subjects, particularly those from the NHLBI-funded ACCESS, SAGA, and Henry Ford Health System studies.

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Outcomes of World Health Organization–defined Severe Respiratory Distress without Shock in Adults in Sub-Saharan Africa

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Supported by NIH from grant U01AI150508 (C.C.M. and M.C.).

Author and Investigator Contributions: B.H.C., M.C., and C.C.M. contributed to the conception and design of the study and drafted the manuscript. S.A.A., A.A.M., B.A., M.A.A., T.B., P.B., J.A.C., M.P.G., M.A.M.H., S.T.J., O.D.J., J.K., A.M., M.R., J.R., J.S., R.S., and I.W. contributed to data acquisition and edited the manuscript. E.R.M. contributed to data analysis and edited the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202304-0684LE on July 24, 2023

This letter has a related editorial.

To the Editor:

Sepsis is the leading cause of global mortality and is most often attributed to lower respiratory tract infections and subsequent acute respiratory distress syndrome (ARDS) (1). The greatest burden of sepsis rests on sub-Saharan Africa, where lower respiratory tract infections account for approximately 390,000 adult deaths each year (2). However, patients from sub-Saharan Africa are underrepresented in sepsis and ARDS research (3).

ARDS is difficult to diagnose in low-income countries because it requires often unavailable imaging, mechanical ventilation to set positive end-expiratory pressure and deliver a reliable fraction of inspired oxygen, and arterial blood gases to identify hypoxemia (4). To mitigate this gap, the World Health Organization (WHO) pragmatically defined severe respiratory distress without shock (SRD) in adults as oxygen saturation of less than 90% or a respiratory rate of more than 30 breaths per minute, and a systolic blood pressure over 90 mm Hg in the setting of infection and in the absence of clinical cardiac failure (5). The natural history of SRD has not been fully described; accordingly, we aimed to evaluate the prevalence, characteristics, and outcomes of SRD in hospitalized patients in sub-Saharan Africa.

Methods

We conducted a multi-cohort analysis using previously collected deidentified data pooled from 16 hospital-based studies, which were conducted in six countries throughout sub-Saharan Africa from 2009 through 2019, including one previously unpublished dataset (Kitovu Hospital, Masaka, Uganda) (Table 1) (6). Variables in the pooled dataset included: admission age, sex, temperature, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, oxygen saturation, Glasgow coma scale (GCS) score, and HIV serostatus. The pooled dataset did not include causes of infection for all participants. We defined SRD according to WHO criteria with the exception of the exclusion of heart failure. We excluded patients younger than 14 years of age. We imputed missing data using multiple imputation with chained equations with 10 iterations (7). We did not impute sex, HIV serostatus, or mortality. We used Stata 13.0 (Stata) and SAS Version 9.4 (SAS Institute) for all analyses.

We determined the associations of respiratory rate and oxygen saturation with mortality in separate univariate analyses. We constructed multivariable baseline risk models of in-hospital mortality in all participants and in a subset with infection, using logistic regression models that included *1*) age and sex; *2*) age, sex, and HIV serostatus; *3*) age, sex, and GCS score; and *4*) age, sex, HIV serostatus, and GCS score (1). We created separate models for each study with the same variables, but with study-specific coefficients, and then aggregated the models. We included study-specific models with missing baseline variables, such as HIV serostatus, in the aggregate models with the missing variable deleted. We determined the area under the receiver operating characteristic curve (AUC) and absolute

Table 1. Data from Hospital-based Cohort Studies Conducted in Six African Countries from 2009 through 2019

Study	Year	Site	Inclusion Criteria	Total (*n*)	In-Hospital Mortality (%)	Average Missing Clinical Data per Patient (%)*	Missing Oxygen Saturation per Study (%)	Missing HIV Data per Study (%)
Adakun	2013	Uganda	Meningitis†	141	28	12	100	0
Amir	2016	Uganda	Sepsis‡	206	31	15	100	1
Andrews	2013	Zambia	Sepsis‡	209	41	15	10	2
Andrews	2014	Zambia	Sepsis‡	109	62	14	30	0
Auma	2013	Uganda	Sepsis§	216	19	13	100	22
Huson	2015	Gabon	Sepsis‖	381	4	13	3	0
Jacob	2009	Uganda	Sepsis‡	381	24	13	100	16
Jacob	2012	Uganda	Sepsis‡	423	25	4	5	0
Majwala	2013	Uganda	Meningitis†	145	32	13	100	0
Opio	2013	Uganda	Hospitalized¶	1,664	7	17	23	66
Roth	2015	Sierra Leone	Fever**	429	19	21	100	94
Rubach	2015	Tanzania	Fever††	400	11	1	1	3
Rylance	2009	Tanzania	Hospitalized¶	694	11	6	16	100
Ssekitoleko	2011	Uganda	Sepsis§	150	30	13	100	13
Wheeler	2013	Malawi	Hospitalized¶	355	23	2	0	19
Unpublished	2019	Uganda‡‡	Hospitalized¶	1,482	7	4	1	4
Total	—	—	—	7,385	15	10	39	33

The data from these hospital-based cohort studies contributed to pooled data for the analysis of the prevalence, characteristics, and outcomes of World Health Organization–defined severe respiratory disease without shock.
*Clinical data include temperature, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and Glasgow Coma Scale score.
†Admitted with a clinical diagnosis of meningitis.
‡Admitted with a clinical diagnosis of severe sepsis, defined as systemic inflammatory response syndrome with suspected infection and organ dysfunction.
§Admitted with a clinical diagnosis of sepsis defined as systemic inflammatory response syndrome with suspected infection.
‖Admitted with a temperature ⩾38°C or <36°C and at least one other systemic inflammatory response syndrome criterion.
¶Admitted with an acute illness to a medical ward with no other specified inclusion criteria.
**Admitted with subjective fever or had a documented temperature ⩾38°C within 24 hours of admission.
††Admitted with a temperature ⩾38.0°C.
‡‡Kitovu Hospital, Masaka, Uganda.

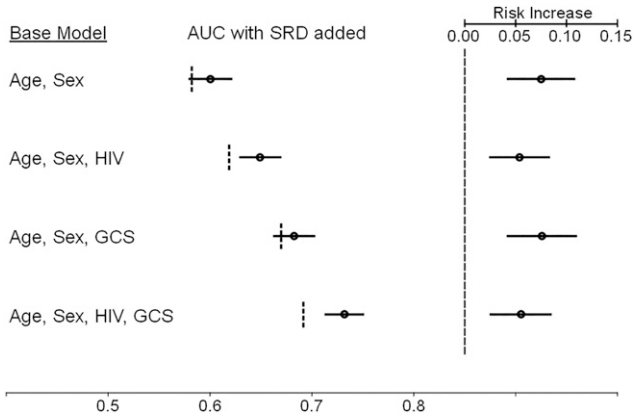

Figure 1. Comparison of the area under the receiver operating characteristic curve (AUC) for in-hospital mortality models with and without the inclusion of admission severe respiratory disease (SRD), as defined by the World Health Organization, and the estimated mortality risk increases associated with the incorporation of SRD in each model. (Left) Each baseline risk model is provided, followed by the AUC calculated for each model. Vertical dotted lines represent the AUC for each base model. The black dot and horizontal line represent the AUC and 95% confidence interval when SRD is included as an independent variable for each base model. The AUC values are provided according to the scale at the bottom of the figure. (Right) The vertical dashed line at right represents the baseline mortality risk for each model. The black dot and horizontal line represent the estimated absolute mortality risk increase and 95% confidence interval when SRD is present in each base model. The values for the estimated absolute risk increase are provided according to the scale at the top of the figure. GCS = Glasgow Coma Scale score.

risks for mortality for each baseline model, with and without the inclusion of admission SRD as an independent variable.

Results

Of the 7,385 participants, the median age was 37 years (interquartile range [IQR], 27–53), 3,584 (49%) were female, and 2,282 (46%) of the 4,917 participants with a known HIV serostatus were living with HIV. The median respiratory rate was 24 (IQR, 20–30) breaths per minute. Among the 5,121 participants with oxygen saturation recorded, the median value was 96% (IQR, 94–98%).

There were 949 (13%) participants with SRD. Among the 3,575 participants admitted to the hospital with an infection, 578 (16%) had SRD, compared with 371 (10%) of 3,810 participants with undifferentiated causes of hospital admission (odds ratio [OR], 1.78; 95% confidence interval [CI] = 1.55–2.06). Among participants with SRD, the median (and IQR for) oxygen saturation and respiratory rate were 91% (85–97%) and 35 (31–40) breaths per minute, respectively; 235 (25%) met the criterion of oxygen saturation $<$90% only, 610 (64%) met the criterion of respiratory rate $>$30 breaths per minute only, and 104 (11%) met both criteria.

In-hospital mortality occurred in 1,096 (15%) participants. Among participants with SRD, 209 (22%) died in hospital, compared with 887 (14%) of 6,436 participants without SRD (OR, 1.77; 95% CI = 1.49–2.10). The in-hospital case fatality ratio for participants meeting the SRD criteria of respiratory rate only, oxygen saturation only, or both was 111 (18%) of 610, 55 (23%) of 235, and 43 (41%) of 104, respectively ($P < 0.001$ across groups). In all participants, for every increase of 10 breaths per minute, there was a 75% increase in the odds of mortality (OR, 1.75; 95% CI = 1.64–1.87), and for every 1% increase in oxygen saturation, there was an 8% reduction in the odds of mortality (OR, 0.92; 95% CI = 0.91–0.93). In participants with SRD, there was a nonstatistically significant increase in odds of mortality associated with increased respiratory rate (OR, 1.13; 95% CI = 0.96–1.33), and for every 1% increase in oxygen saturation, there was a 6% reduction in the odds of mortality (OR, 0.94; 95% CI = 0.92–0.96). Using the imputed data, across baseline multivariable models, we found that AUCs ranged from 0.58 to 0.69, which increased, with the addition of SRD, to 0.60 to 0.73. The presence of SRD in the models increased the absolute risk of mortality by 5.4–7.5% over the baseline risk ($P < 0.001$ for all models) (Figure 1). In participants with infection, the presence of SRD in the models increased the absolute risk for mortality by 2.5–3.7%.

Discussion

In the first comprehensive evaluation of the prevalence, characteristics, and outcomes of WHO-defined SRD in hospitalized patients in sub-Saharan Africa, we found that SRD was common with a prevalence that ranged from 10 to 16%, depending on whether the participant was admitted with infection or not. SRD was associated with a high in-hospital case fatality ratio of 22%. Increases in respiratory rate were associated with an increased risk of in-hospital mortality, whereas increases in oxygen saturation were associated with decreased risk of in-hospital mortality. The presence of SRD in each baseline model increased the AUC and the associated absolute risk of mortality. We were limited by missing data but accounted for this by using a robust imputation strategy. We were also unable to rule out heart failure; however, our findings were similar in a sensitivity analysis of participants with infection. We were not able to directly compare SRD to ARDS diagnoses, nor is this likely to be done on a large scale, because of the resource constraints that limit the ability to diagnose ARDS in low-income settings, even when using the less resource-intensive Kigali modification of the Berlin ARDS criteria (8). Nonetheless, our data suggest that SRD identifies patients with acute respiratory disease who are at high risk of death, making SRD a reasonable proxy for ARDS in clinical settings where the components needed for a diagnosis of ARDS are unavailable. Prospective multisite studies could provide further data about the case incidence, etiologies, and outcomes of SRD in Africa. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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The Race Arithmetic of the Global Lung Function Initiative Global Reference Equations

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Supported by a grant from the NHLBI (K23HL162593).

Originally Published in Press as DOI: 10.1164/rccm.202303-0565LE on May 16, 2023

To the Editor:

I commend Bowerman and colleagues and the Global Lung Function Initiative (GLI) on advocating for the non–race-based application of a single set of spirometry reference equations rather than the use of different reference equations for persons of different races (1). However, I am troubled by the method used to derive the GLI Global reference equations, notably *1*) the uncritical use of racial categories to apportion sample weights, *2*) the lack of justification for selecting sample weights, and *3*) the apparent discrepancy between the weighting strategy described in the Methods section and the actual weights reported in the online supplement.

Recent studies have suggested that the use of race-specific reference equations does not yield superior clinical utility compared with the non–race-based application of the GLI Other reference equations (2–4). However, Bowerman and colleagues express concern that the GLI Other reference equations—initially intended for application to self-identified multiracial persons or populations not represented in the GLI 2012 dataset—privilege the relatively greater contribution of observations from participants categorized as "Caucasians." "Caucasians" contributed 57,395 (77%) out of 74,187 observations used to derive the GLI Other reference equations. "African Americans" contributed 3,545 observations (5%), "North East Asians" contributed 4,992 observations (7%), and "South East Asians" contributed 8,255 observations (11%) (5).

The authors' proposed solution is to weight observations in the GLI 2012 dataset "such that each group contributes an equal proportion" to the new GLI Global reference equations. This approach, which the authors describe as applying "inverse-probability weights," would weight the data to approximate an ideal population composed equally of "Caucasians," "African Americans," "North East Asians," and "South East Asians." Unfortunately, this approach is arbitrary and invites confusion and misunderstanding. Specifically, I point out the following:

1. This approach presumes the validity of the racial categories constructed by Quanjer and colleagues in 2012 (5) as the appropriate parameter by which to measure sample representativeness. Because race is an ever-changing, context-dependent, and socially, politically, and legally determined classification scheme rather than a measurable, durable, biological designation, the validity of these categories is doubtful, including and especially the notion that "North East Asians" and "South East Asians" represent meaningfully different populations. It is worth recalling that, although observations for the "Caucasian" reference equation came predominantly from the United States, United Kingdom, and Switzerland, the "Caucasian" classification was also applied to observations from locations as disparate as Algeria, Brazil, Chile, Israel, Portugal, Sweden, Tunisia, Uruguay, and Venezuela, among others. Meanwhile, observations for the "African American" reference equations came only from the United States; for the "North East Asian" equations, from northern China and South Korea; and for the "South East Asian" equations, from Hong Kong, Taiwan, and Thailand. The rationale for these categories is described by Quanjer