Outcomes of WHO defined severe respiratory distress without shock in adults in sub-Saharan Africa

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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). Yet 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 gasses 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 <90% or respiratory rate >30 breaths per minute, and a systolic blood pressure >90 mmHg 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 de-identified data pooled from 16 hospital-based studies, which were conducted in 6 countries throughout sub-Saharan Africa from 2009 through 2019 including 1 previously unpublished dataset (Kitovu Hospital, Masaka, Uganda) (Table 1) (6).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 human immunodeficiency virus (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

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excluded patients <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 and SAS 9.4 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 logisitc regression models that included: 1) age, sex; 2) age, sex, HIV; 3) age, sex, GCS; and 4) age, sex, HIV, GCS (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, e.g. HIV serostatus, in the aggregate models with the missing variable deleted. We determined the area under the curve (AUC) and absolute risks for mortality for each baseline model with and without the inclusion of admission SRD as an independent variable.

Results

Of the 7385 participants, the median age (interquartile range [IQR]) was 37 (27-53) years, 3584 (49%) were female, and 2282 (46%) of the 4917 with a known HIV serostatus were living with HIV. The median (IQR) respiratory rate was 24 (20-30) breaths per minute. Among the 5121 participants with oxygen saturation recorded, the median (IQR) value was 96% (94-98%).

There were 949 (13%) participants with SRD. Among the 3575 participants admitted to the hospital with an infection, 578 (16%) had SRD compared to 371 (10%) of 3810 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 (IQR) oxygen saturation and respiratory rate were 91% (85-97%) and 35 (31-40) breaths per minute, respectively; 235 (25%) met the

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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 death occurred in 1096 (15%) participants. Among participants with SRD, 209 (22%) died in hospital compared to 887 (14%) of 6436 participants without SRD (OR 1.77, 95% CI 1.49-2.10). The in-hospital case fatality ratio for participants meeting 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 death (OR 1.75, CI 1.64-1.87), and for every 1% increase in oxygen saturation there was an 8% reduction in the odds of in-hospital mortality (OR 0.92, CI 0.91-0.93). In participants with SRD, there was a non-statistically significant increase in odds of death associated with increased respiratory rate (OR 1.13, CI 0.96-1.33), and for every 1% increase in oxygen saturation there was a 6% reduction in the odds of in-hospital mortality (OR 0.94, CI 0.92-0.96). Using the imputed data, across baseline multivariable models, 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 increased risk of in-hospital death, while increases in oxygen saturation were associated with decreased risk of in-hospital death. The

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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 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 due to 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 multi-site studies could provide further data about the case incidence, etiologies, and outcomes of SRD in Africa.

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Table 1. Hospital-based cohort studies conducted in six African countries from 2009-2019 contributing to pooled data for the analysis of the prevalence, characteristics, and outcomes of World Health Organization defined severe respiratory disease without shock.

Study	Year	Site	Inclusion criteria	Total (n)	In-hospital mortality (%)	Average missing clinical data per patient (%)[a]	Missing oxygen saturation per study (%)	Missing HIV per study (%)
Adakun	2013	Uganda	Meningitis[d]	141	28%	12%	100%	0%
Amir	2016	Uganda	Sepsis[e]	206	31%	15%	100%	1%
Andrews	2013	Zambia	Sepsis[e]	209	41%	15%	10%	2%
Andrews	2014	Zambia	Sepsis[e]	109	62%	14%	30%	0%
Auma	2013	Uganda	Sepsis[f]	216	19%	13%	100%	22%
Huson	2015	Gabon	Sepsis[g]	381	4%	13%	3%	0%
Jacob	2009	Uganda	Sepsis[e]	381	24%	13%	100%	16%
Jacob	2012	Uganda	Sepsis[e]	423	25%	4%	5%	0%
Majwala	2013	Uganda	Meningitis[d]	145	32%	13%	100%	0%
Opio	2013	Uganda	Hospitalized[h]	1,664	7%	17%	23%	66%
Roth	2015	Sierra Leone	Fever[i]	429	19%	21%	100%	94%
Rubach	2015	Tanzania	Fever[j]	400	11%	1%	1%	3%
Rylance	2009	Tanzania	Hospitalized[h]	694	11%	6%	16%	100%

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Ssekitoleko	2011	Uganda	Sepsis[f]	150	30%	13%	100%	13%
Wheeler	2013	Malawi	Hospitalized[h]	355	23%	2%	0%	19%
Unpublished	2019	Uganda[k]	Hospitalized[h]	1,482	7%	4%	1%	4%
Total	---	---	---	7385	15%	10%	39%	33%

a=Clinical data include temperature, heart rate, respiratory rate, SBP, DBP, and GCS
b=Laboratory data include WBC count, hemoglobin concentration and platelet concentration
c=CD4 counts are only reported for HIV-infected patients
d=Admitted with a clinical diagnosis of meningitis
e=Admitted with a clinical diagnosis of severe sepsis defined as systemic inflammatory response syndrome with suspected infection and organ dysfunction
f=Admitted with a clinical diagnosis of sepsis defined as systemic inflammatory response syndrome with suspected infection
g=Admitted with a temperature ≥38 or <36 °C and at least one other systemic inflammatory response syndrome criterion
h=Admitted with an acute illness to a medical ward with no other specified inclusion criteria
i=Admitted with subjective fever or or had a documented temperature ≥ 38°C within 24 hours of admission
j=Admitted with a temperature ≥ 38.0°C
k=Kitovu Hospital, Masaka, Uganda

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Figure legend

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 (WHO), and the estimated mortality risk increases associated with the incorporation of SRD in each model. At left, each baseline risk model is provided followed by the AUC calculated for each model. The 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 to each base model. The values for AUC are provided according to the scale at the bottom of the figure. At right, the black dot and horizontal line represent the estimated absolute risk increase and 95% confidence interval when SRD is present in each base model. The vertical dashed line at right represents the baseline mortality risk for each 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; HIV = human immunodeficiency virus.

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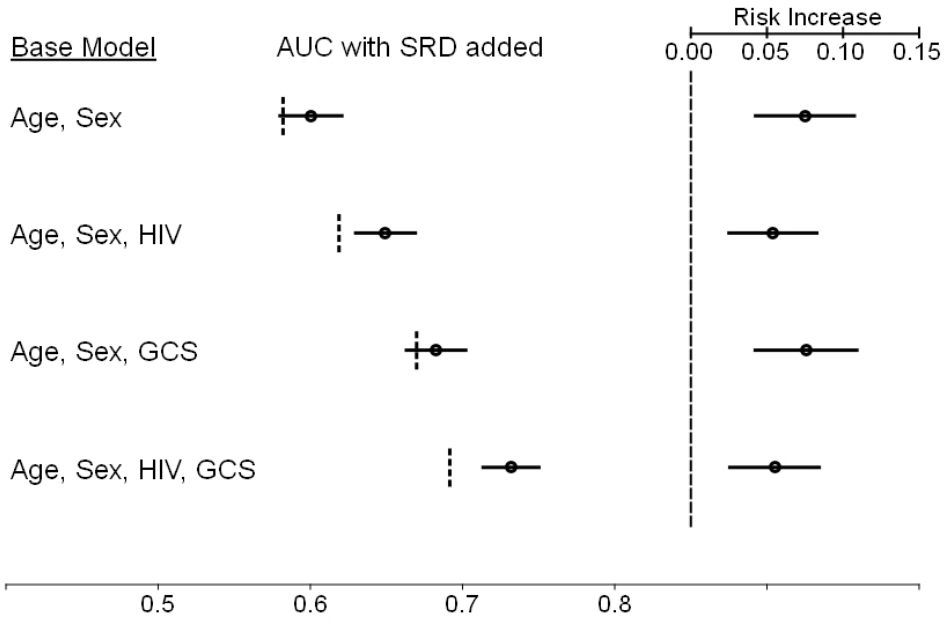

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