The saturation gap: a simple transformation of oxygen saturation using virtual shunt

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ABSTRACT

Objective Peripheral oxygen saturation (SpO_2) obtained from pulse oximetry is a widely used physiological measurement. Clinical interpretation is limited by the nonlinear relationship between SpO_2, degree of impairment in gas exchange, and effect of altitude. SpO2 is frequently dichotomized to overcome these limitations during prediction modelling. Using the known physiological relationship between virtual shunt and SpO_2, we propose the *saturation gap* as a transformation of SpO_2.

Approach We computed the theoretical virtual shunt corresponding to various SpO_2 values and derived an accurate approximation formula between virtual shunt and SpO_2. The approximation was based on previously described empiric observations and known physiological relationships. We evaluated the utility of the *saturation gap* in a clinical study predicting the need for facility admission in children in a rural health-care setting.

Main Results The transformation was *saturation gap* = $49.314*\log_{10}(103.711 - SpO_2) - 37.315$. The ability to predict hospital admission based on a continuous variable SpO_2 or *saturation gap* produced an identical area under the curve of 0.71 (95% CI: 0.69-0.73), compared to only 0.57 (CI: 0.56-0.58) based on diagnosis of hypoxemia (defined as SpO_2<90%). However, SpO_2 demonstrated a lack of fit compared to *saturation gap* (goodness-of-fit test p-value <0.0001 versus 0.098). The observed admission rates varied linearly with *saturation gap* but varied nonlinearly with SpO_2.

Significance The *saturation gap* estimates a continuous linearly interpretable disease severity from SpO_2 and improves clinical prediction models. The *saturation gap* will

also allow for straightforward incorporation of altitude in interpretation of measurements of SpO_2.

INTRODUCTION

Virtual shunt (VS) is a theoretical concept that describes the overall loss of oxygen content between the inspired gas and the arterial blood. Estimating VS is useful as the magnitude of VS quantitatively describes the efficiency of the gas exchange and the severity of a disease process that may lead to hypoxemia. The concept of VS was initially used to describe the non-linear relationship between inspired oxygen (FiO_2) and the arterial partial pressure of O_2 (PaO_2) using iso-shunt curves [1]. VS can be defined as the proportion of blood that would need to bypass the lungs to produce the difference between the calculated end capillary venous oxygen content and arterial blood oxygen content and is also known as venous admixture.

VS is typically calculated based on assumed values of the arterial/mixed venous oxygen content difference, hemoglobin level, pH and temperature unless these values can be measured [2, 3]. A more common formula, the difference between the oxygen partial pressure in the alveoli (PAO_2) and systemic arteries (PaO_2) (P[A-a] O_2), has been used to represent the shunt calculation. This formula does adjust for changes in

FiO_2 (due to changes in altitude or oxygen administration) but has the inherent limitations of the requirement of performing an invasive measurement to obtain PaO_2 and uses partial pressure instead of oxygen content that is not linearly related to the degree of gas exchange abnormality [2-4].

Our objective is to propose a simple transformation of SpO_2, the *saturation gap*, which is linearly related to the degree of impairment in oxygen exchange and that can be adjusted for FiO_2. The transformation is based on the known empiric and physiological relationship between VS and SpO_2 and is aimed to address the nonlinearity in hemoglobin-oxygen dissociation curves. Despite the number of assumptions made in the estimation of the *saturation gap*, we evaluate the clinical and statistical value compared to using the observed SpO_2.

METHODS

Physiological calculation of VS

Following Karlen W, et al [2, 3], we derive VS from inspired oxygen FiO_2 and arterial oxygen saturation (SaO_2) for *a theoretical subject* that satisfies the following assumptions.

- The loss due to capillary diffusion is negligible, which allows alveoli oxygen

content (PAO_2) to be well approximated by end-capillary oxygen content.

- SaO_2 is estimated without error from SpO_2 obtained from pulse oximetry.
- Patients are on room air at the time of SpO_2 measurements. The barometric pressure is at sea level (101 kPa) and inspired oxygen (FiO_2) is at 21%.
- Normal constant values for water vapor pressure, alveolar CO_2 partial pressure, respiratory quotient, incomplete capillary diffusion, arterio-venous oxygen difference, oxygen-binding capacity of hemoglobin, blood concentration of hemoglobin, and solubility of O_2 in hemoglobin are used.

Under the above assumptions, we can *theoretically* calculate the VS using simultaneous equations previously established [5-7]. PAO_2 was estimated using the Alveolar Gas Equation [5]. Alveoli oxygen concentration (SAO_2) was then estimated from PAO_2 using the Severinghaus equation [6]. To calculate arterial oxygen content, SaO_2 was transformed to PaO_2 using the Severinghaus-Ellis equation [6-7]. The detailed mathematical descriptions of the above calculation can be found in the online supplementary material or in Karlen W, *et al* [2, 3].

Saturation Gap

To produce a simple and more clinically useful method to describe the non-linear relationship between VS and SpO_2, we fitted several common nonlinear functions, such as polynomials and logarithmic functions. The unknown parameters of these

functions were estimated using the nonlinear least squares method [8]. For this fitting process, we selected SpO_2 at 1% intervals in the range from 50% to 98% and theoretically estimated VS. The empiric formula is not valid for SpO_2 values above 98%. We also excluded SpO_2 values below 50% as they are rare and typically associated with severe clinical cyanosis. A similar process was used to fit changes in FiO_2 based on theoretical changes in altitude in a range of 0 to 4000m.

The *saturation gap* was then defined as a linearly rescaled version of VS that was fitted to SpO_2 (with changes in FiO_2). This linear rescaling ensured that the *saturation gap* represents the difference between the predicted and observed SpO_2 but not in the same units or direction of change to avoid confusion. We think that this linear rescaling will make the *saturation gap* easier to comprehend for clinicians unfamiliar with the non -linearity of SpO_2 or the concept of VS and therefore extend its practical utility.

Application to Prediction Performance

We evaluated the use of the *saturation gap* compared to SpO_2 in a recently completed prospective observational study at the Kumudini Women's Medical College Hospital's in Bangladesh, a rural tertiary care hospital [9]. Ethics approval and informed consent were obtained prior to data collection.

The study aimed to develop a simple model to predict the need for facility admission that could be used in a community setting. Children < 5 years of age presenting at the outpatient or emergency department were enrolled. Study physicians collected clinical signs and symptoms from the facility records and performed recordings of SpO_2, heart rate and respiratory rate. Facility physicians made the decisions about the need for hospital admission and they were blinded to the oxygen saturation measurements. SpO_2 was taken as the median over a minute at the time of initial assessment. SpO_2 readings above 98% were considered to be equal to 98%, for 98% is the theoretical maximum reading on room air at sea level. Readings above 98% occurred due to the tolerance level or bias of the pulse oximeters [2, 3]. Children who showed high SpO_2 variability (range>6%) in combination with low perfusion were not included. Motion artifact, ambient light and poor positioning of the sensor typically resulted in high variability and low perfusion leading to a high likelihood of artificial SpO_2 readings. Low perfusion was assessed post-hoc by analyzing the amplitude of the photoplethysmogram and consulting the provided perfusion index (low/medium/high) by the pulse oximeter device. Children with SpO_2 below 75% (a danger sign) were also excluded from predictive modeling, for they were considered critically ill and should be directly admitted into higher-level facilities regardless of any model based predictions [10].

We fitted three univariate logistic regression models to predict the need for facility admission: 1) hypoxemia, defined as SpO_2<90% by the World Health Organization, (hypoxemia model), 2) observed SpO_2 (SpO_2 model), and 3) the *saturation gap* (saturation gap model). We compared these models in terms of overall accuracy, calibration and clinical interpretation. Overall accuracy was assessed using the area under the receiver operating characteristic curve (AUC ROC) and its 95% confidence interval (CI). AUC measured the probability that a randomly selected admitted child would receive a higher predicted probability of requiring admission than a randomly selected child who was not admitted [11]. For the SpO_2 model and the saturation gap model, calibration was assessed by plotting the observed admission rate against the group average of the predicted probability of requiring admission for each of 3 groups determined a priori: SpO_2<90%, SpO_2 from 90% to 97.5% and SpO_2 equal to 98%. A chi-square goodness-of-fit test was then applied [12]. In addition, the observed admission rates were plotted against 10 equally spaced SpO_2 or 10 equally spaced saturation gap categories sharing similar ranges. The plots were fitted to linear and nonlinear trends using the method of least squares [8], which aimed to minimize the total squared difference between the observed admission rates and the risks of admission directly interpreted from the category-average SpO_2 or saturation gap levels. The accuracy of the fitted relationship was quantified by the standard deviations of the difference between the observed admission rates and the interpreted risks of admission based on the SpO_2 or *saturation gap* category labels. The 95% CIs for these standard deviations were calculated based on chi-square distributions [8].

Altitude Adapted Saturation Gap

The transformation of SpO_2 to the saturation gap could be extended to incorporate the variations of the normal SpO_2 with altitude using the following three steps

Step 1) theoretically calculating VS for various altitudes using the methods described in Karlen W, et al [2, 3],

Step 2) approximating the theoretical VS from SpO_2 using formulas with altitude-specific coefficients and

Step 3) linearly rescaling the formula estimated VS [8].

RESULTS

Physiological Calculation of VS

Due to the empirical nature of the physiological equations [5-7], the VS corresponding to SpO_2 98% was a small negative value (-0.78). We thus added 0.78 to all VS values so that a normal SpO_2 98% corresponded to exactly zero VS.

The Transformation Formula for the Saturation Gap

The functions of the form $y = a*\log_{10}(b - x) + c$ were sufficient to capture the non-linearity in the relationship between physiological VS and SpO_2. The relationship was statistically best fitted by an equation $VS = 68.864*\log_{10}(103.711 - SpO_2) - 52.109$ (Figure 1). The *saturation gap* was therefore defined as *saturation gap* = 0.716* *VS* +1.078= $49.314*\log_{10}(103.711 - SpO_2) - 37.315$. The *saturation gap* varied from 48%

to 0% when SpO_2 varied from 50% to 98%.

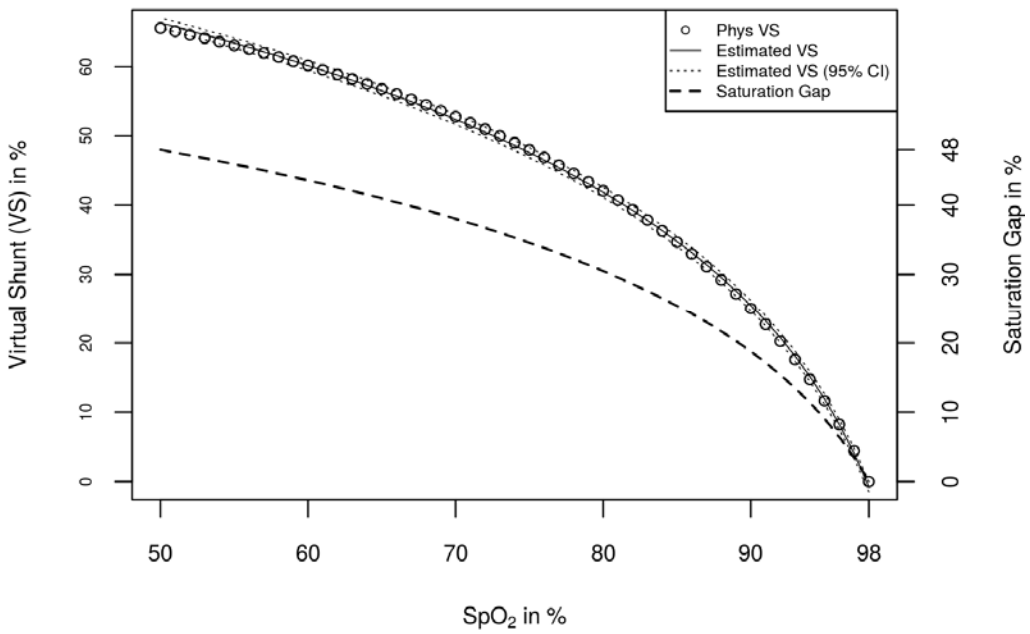

Figure 1: Scatterplot of the estimated virtual shunt (%) and the *saturation gap* (%) against observed SpO_2 (%). "Phys VS" is the shunt estimated by solving simultaneous equations using multiple physiological variables, "Estimated VS" is the shunt computed using the simpler algebraic transformation "Estimated VS = $68.864*\log_{10}(103.711 - SpO_2) - 52.109$". The standard deviation of the differences between "Phys VS" and "Estimated VS" is 0.37%, indicating that 95% of the differences between "Estimated VS" and "Phys VS" are within 0.74%.

Prediction Performance and Model Calibration

In total, 2943 of the 3374 recruited cases had adequate SpO_2 recordings, of whom 831 were admitted and 2112 were not admitted. We excluded 5 cases showing SpO_2

variability > 6% in combination with low perfusion. We adjusted the 868 SpO_2 readings above 98% to be equal to 98%. The 12 cases with SpO_2<75% were all admitted and they were excluded from predictive modeling.

The distribution of observed SpO_2 and that of the *saturation gap* revealed more informative discrimination of the outcome group than that of hypoxemia (Figure 2). In addition, the distribution of the *saturation gap* was less skewed (skewness 2.26 vs -3.54 for the admitted and 0.98 vs -2.84 for the not admitted cases) than that of observed SpO_2 (Figure 2).

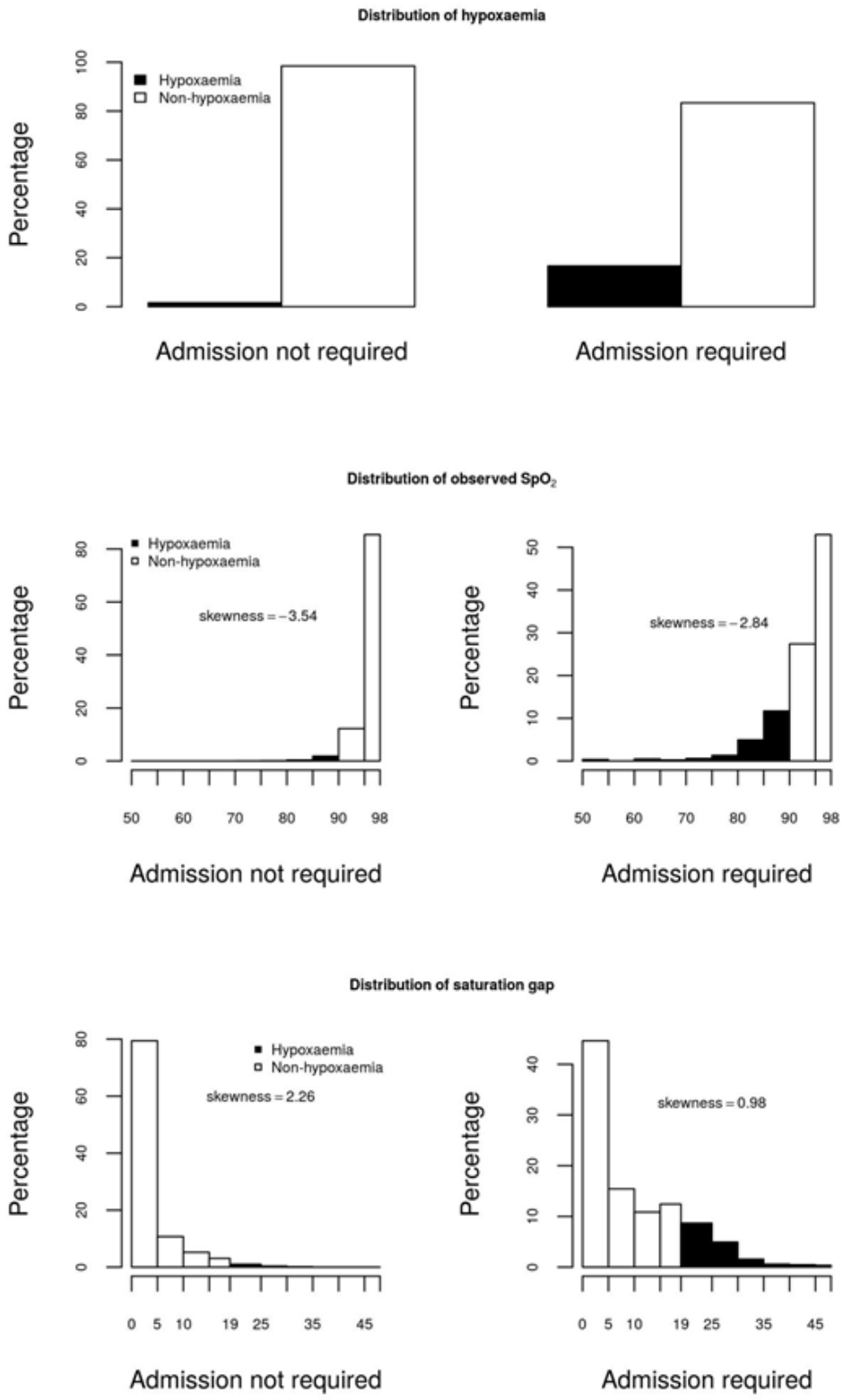

Figure 2: Distribution of hypoxemia, SpO_2 (%) and the *saturation gap* (%) by

outcome group.

The hypoxemia model, the SpO_2 model and the *saturation gap* model all demonstrated that a SpO_2 below 90% was associated with increased risk of admission and the latter two, unsurprisingly had a much higher AUC (Table 1). Despite the identical AUC, the SpO_2 model demonstrated a statistically significant lack of fit (p-value <0.0001, χ^2=19.973, df=1) whereas the *saturation gap* model did not (p-value =0.098, χ^2=2.744, df=1). A closer look at the data revealed that the SpO_2 model significantly underestimated the risk of admission among the 1017 children with SpO_2 between 90% and 97.5% and significantly overestimated the risk of admission among the 1750 children with SpO_2 98% (Figure 3). Therefore, the saturation gap model was better calibrated than the SpO_2 model. In terms of clinical interpretation, a 5% decrease in SpO_2 and a 5% increase in the saturation gap were respectively predicted to be associated with a 286% and 84% increase in the odds of requiring admission (Table1). The magnified odds ratio obtained from the SpO_2 model was due to the dense distribution of SpO_2 data between 85% and 98% (Figure 2) and that in this region a 5% decrease in SpO_2 corresponded to a more than 5% increase in the *saturation gap* (Figure 1).

Table 1: Summary of the three prediction models for the need of facility admission

Model	**Odds ratio (95% CI)**	**AUC ROC (95% CI)**
Hypoxemia model	11.47 (7.74-16.99)[a]	0.57 (0.56-0.58)
SpO_2 model	3.86 (3.31-4.50)[b]	0.71 (0.69-0.73)
Saturation gap model	1.84 (1.73-1.96)[c]	0.71 (0.69-0.73)

a. associated with changing from the absence of hypoxemia to the presence of hypoxemia

b. associated with a 5% decrease in SpO_2

c. associated with a 5% increase in the *saturation gap*

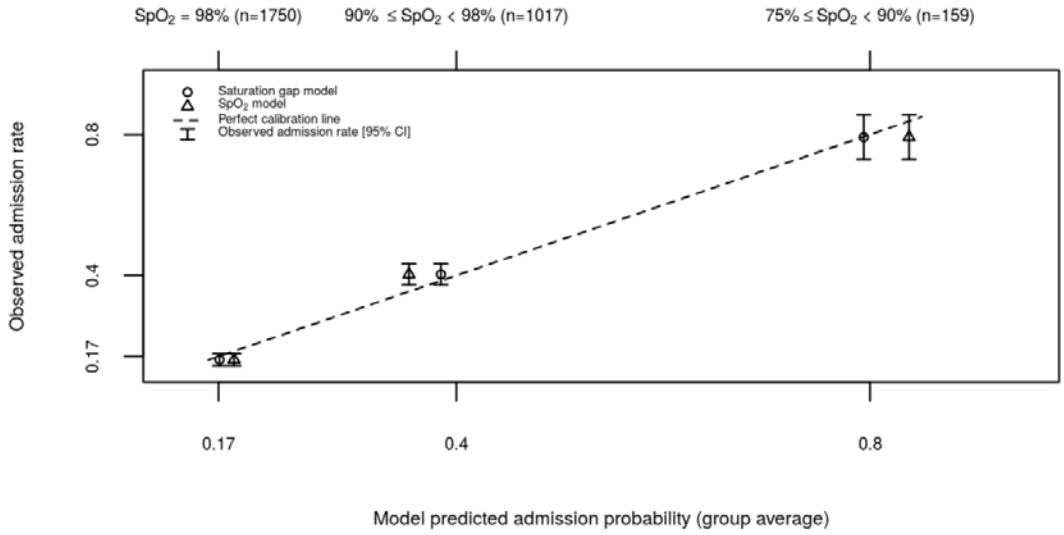

Figure 3: Calibration plot of the SpO_2 model and the *saturation gap* model applied to

the 2926 cases with SpO_2 above or equal to 75%. The dotted line is the line of equality on which model predicted admission probabilities perfectly coincide with observed admission rates.

The observed admission rates exhibited a nonlinear relationship with SpO_2 but an approximately linear relationship with saturation gap (Figure 4). More specifically, each 3% increase in saturation gap was associated with an approximately 8.2% increase in the admission rate. In contrast, each 2% decrease in SpO_2 would be associated with *varying* increases in the admission rate due to the nature of the nonlinear trend in Figure 4.

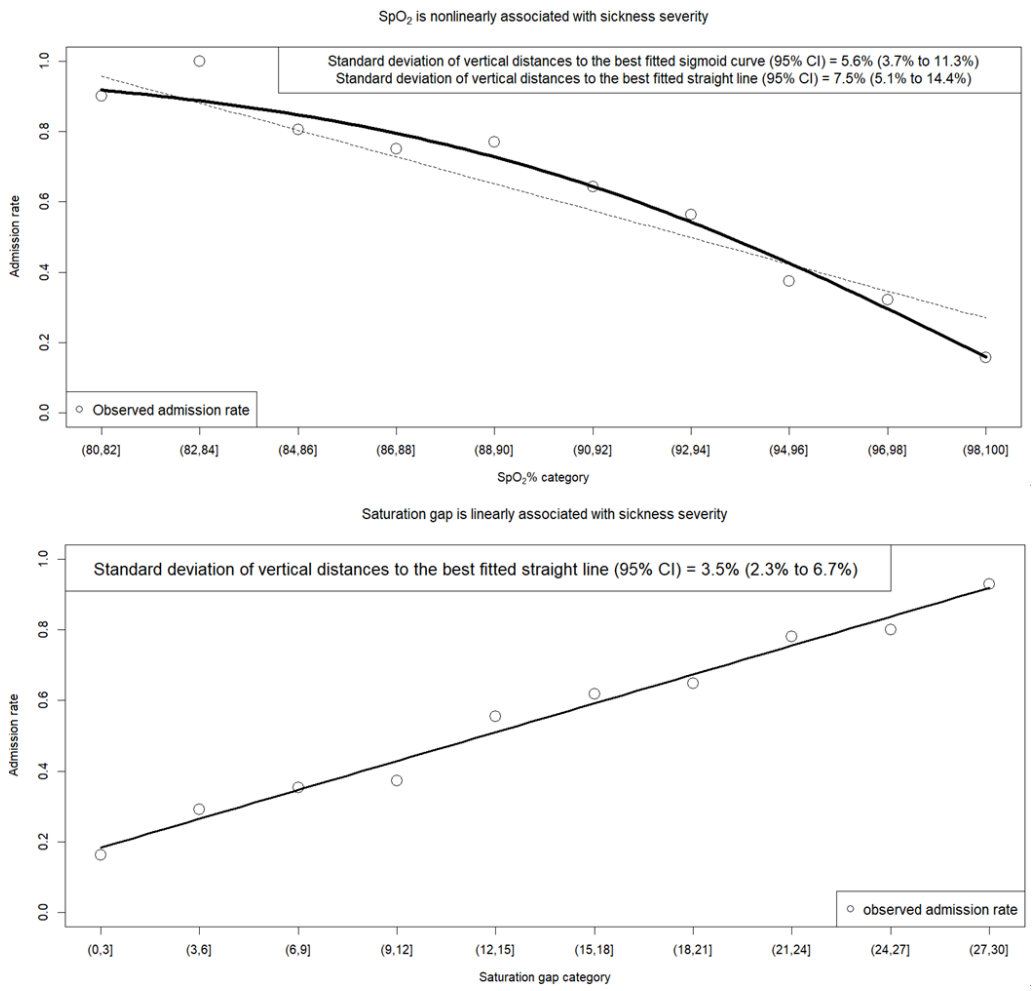

Figure 4: Observed admission rates compared to equally spaced SpO_2 and saturation gap categories. Each category includes the right endpoint but excludes left endpoint (e.g. 80-82 includes SpO_2=82% but excluded SpO_2=80%). For the curve-fitting, the categories are coded from 1 to 10. For SpO_2, the best fitted sigmoid curve (a common type of nonlinear curves for S-shaped relationships) corresponds to an equation $y = 0.980 - 2.138/(1+ e^{-0.266*(x-11.073)})$.

Altitude Adapted Saturation Gap

The previously derived formula $VS = 68.864*log_{10}(103.711 - SpO_2) -52.109$ is as a

special case of the formula $VS = a*log_{10}(b - SpO_2) - c$ in which the coefficients *a*, *b* and *c* are determined from altitude as tabulated in Table 2. Figure 5 shows that the formula yields estimated VS highly close to the physiologically calculated VS for a theoretical subject for altitudes ranging from sea level to 4000 meters.

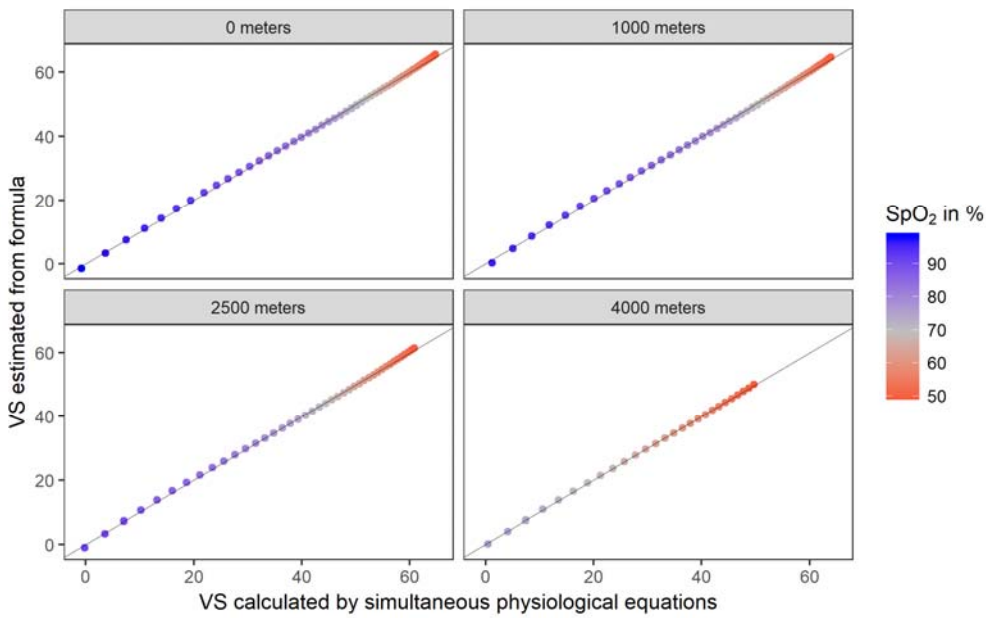

Figure 5: VS estimated from the simple formula against VS calculated by solving simultaneous physiological equations for various altitudes and SpO_2, the solid line represents the line of identity

Table 2: Altitude specific coefficients in the formula to estimate VS and in the formula to define altitude adaptive saturation gap

Altitude in meter	*Coefficients to estimate VS*			*Coefficients to obtain adaptive saturation gap*		
	a	*b*	*c*	*A*	*b*	*C*

0	68.9	103.7	52.1	49.3	103.7	37.3
500	69.4	103.1	54.6	52.1	103.1	40.2
1000	70.2	102.3	56.0	52.4	102.3	42.0
1500	71.6	101.4	58.5	53.1	101.4	42.9
2000	72.3	99.8	59.8	55.6	99.8	46.3
2500	74.4	97.9	63.5	57.1	97.9	47.9
3000	75.4	94.6	65.1	62.5	94.6	55.2
3500	79.5	90.8	72.2	66.6	90.8	59.3
4000	83.3	84.7	78.4	80.1	84.7	75.5

The altitude adaptive saturation gap is set to be $A*log_{10}(b - SpO_2) - C$ with the coefficients *A*, *b* and *C* determined from altitude as tabulated in Table 2. The altitude adaptive saturation is always 0% for a maximum normal SpO_2 (which varies with altitude) and is always 48% for a SpO_2 of 50%.

DISCUSSION

The transformation of the SpO_2 to the *saturation gap* improves clinical interpretation, accuracy and calibration of prediction models. The *saturation gap* will have additional importance in estimating severity of disease and response to treatment (such as oxygen administration) since it incorporates the nonlinearity in hemoglobin-oxygen

dissociation curves. Small changes in SpO_2 on the flat portion of the oxygen saturation curve (near 100%) reflect a much greater change in physiology than the same change at a lower SpO_2. In contrast, the saturation gap is *linearly* related to the changes in the physiological and clinical state. For example, on the scale of SpO_2, a decrease from 95% to 90% would reflect more impairment in gas exchange, and therefore may indicate more significant change (deterioration in clinical condition), than a decrease from 90% to 85%. This nonlinear interpretability of SpO_2 is particularly undesirable when it is used as a predictor (e.g. in Amatet, *et al* [13]), whether in univariate or multivariate analysis, for interpretations of regression models often involve a description of the average amount of outcome change that will be associated with a given amount of predictor change. Such description is only meaningful if the amount of predictor change is clinically comparable for different baseline values. This has typically been resolved by dichotomizing the SpO2 values. However, the use of continuous predictors has been recommended to prevent information loss and decrease in predictive capability resulting from dichotomization [14]. To improve model interpretability, it would be unwise to use hypoxemia as a surrogate predictor in view of the loss in accuracy. Instead, the use of the *saturation gap* in lieu of observed SpO_2 as a predictor would not only maintain the prediction accuracy but also increase clinical interpretation and calibration of prediction models. The use of equally spaced saturation gap categories also provides a way to *linearly* interpret sickness severity (e.g. hospital admission rate) that is not achievable with the direct use of observed SpO_2. In addition, the transformation of the SpO_2 to the *saturation gap* can incorporate

the altitude-varying nature of normal SpO_2 to provide a convenient measure that is comparable across different altitudes. This simple transformation will facilitate the clinical application of SpO_2 at different altitudes, for example, when defining hypoxemia as “any SpO2 at or below the 2.5th centile for a population of healthy children at a given altitude” [15].

The major limitation of the proposed transformation is that the derivation makes many assumptions about normal clinical conditions. A change in the saturation gap may be a result of changes in other unmeasured variables in the model and may not be a result of abnormal gas exchange. In addition, the impact of changes in altitude or inspired concentration of oxygen requires more investigation. A further limitation is that this study modeled the outcome of admission, which was not necessarily linked to issues of respiratory compromise. This would be artificially associated with lower AUC values than if modeled using a cohort of children being assessed with a presumed respiratory illness. However, since our predictive variables were all based on oxygen saturation, the comparative differences remain internally valid.

In conclusion, the SpO_2 transformed saturation gap provides an intuitive measure of hypoxemia and may prove to be a useful aid in clinical practice when measuring SpO_2 and as a component of clinical prediction models when included with electronic devices (such as mobile phones) that can easily perform the required calculation.

Further validation is necessary prior to adoption into clinical practice.

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COMPETING INTERESTS

The authors confirm that there are no competing interests.

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