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Pulse oximetry for the diagnosis and management of acute respiratory distress syndrome

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The diagnosis of acute respiratory distress syndrome (ARDS) traditionally requires calculation of the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) using arterial blood, which can be costly and is not possible in many resource-limited settings. By contrast, pulse oximetry is continuously available, accurate, inexpensive, and non-invasive. Pulse oximetry-based indices, such as the ratio of pulse-oximetric oxygen saturation to FiO_2 (SpO_2/FiO_2), have been validated in clinical studies for the diagnosis and risk stratification of patients with ARDS. Limitations of the SpO_2/FiO_2 ratio include reduced accuracy in poor perfusion states or above oxygen saturations of 97%, and the potential for reduced accuracy in patients with darker skin pigmentation. Application of pulse oximetry to the diagnosis and management of ARDS, including formal adoption of the SpO_2/FiO_2 ratio as an alternative to PaO_2/FiO_2 to meet the diagnostic criterion for hypoxaemia in ARDS, could facilitate increased and earlier recognition of ARDS worldwide to advance both clinical practice and research.

Introduction

Pulse oximetry monitoring is the standard of care in most hospital settings, but assessment of the severity of hypoxaemia in acute respiratory distress syndrome (ARDS) has traditionally required the measurement of arterial oxygen tension (partial pressure of arterial oxygen; PaO_2) using arterial blood gas analysis. The initial description of ARDS in 1967[1] preceded the patent application for the first modern pulse oximeter by 7 years.[2] Subsequent definitions of ARDS have relied on the ratio of PaO_2 to fraction of inspired oxygen (PaO_2/FiO_2) to quantify the severity of hypoxaemia, with a PaO_2/FiO_2 of less than or equal to 300 mm Hg required for a diagnosis of ARDS.[3–5] Some clinical trials in ARDS, such as PROSEVA, a trial of prone positioning for moderate-to-severe ARDS,[6] have used PaO_2/FiO_2 ratio cutoffs for prognostic enrichment.[7] Thus, among adult patients with ARDS, arterial blood gas measurements are the historical standard for diagnosing and stratifying the severity of hypoxaemia in ARDS. There is increasing interest, however, in the use of non-invasive surrogates to define and manage hypoxaemia in ARDS and other critical illness syndromes.

The use of pulse oximetry as an alternative metric for assessing the hypoxaemia criterion in the diagnosis of ARDS was first introduced in 2007 with the derivation and validation of the ratio of pulse-oximetric oxygen saturation (SpO_2) to FiO_2 (SpO_2/FiO_2).[8] Since then, several other non-invasive pulse oximetry-based indices for diagnosis and risk stratification, such as the oxygen saturation index (OSI)[9,10] and the respiratory rate and oxygenation (ROX) index,[11] have been developed and studied in various populations. Other approaches to imputing the PaO_2/FiO_2 ratio from the SpO_2/FiO_2 ratio have also been developed.[12–14] Pulse-oximetric indices in ARDS have been widely adopted in paediatric medicine and in resource-limited settings. For the clinical definition of paediatric ARDS, the severity of hypoxaemia can be assessed using either arterial blood gas measurements or pulse oximetry, although PaO_2 is the recommended standard.[15] The Kigali modification of the Berlin definition of ARDS includes an SpO_2/FiO_2 ratio of 315 or lower as the hypoxaemia cutoff for ARDS in settings in which an arterial blood gas analysis is not available.[16] Clinical trials have also used the SpO_2/FiO_2 ratio or imputed the PaO_2/FiO_2 ratio for enrolment and as outcomes.[17,18] Measurement of hypoxaemia with pulse oximetry is of particular interest given a recent proposal

Key messages

- Measurement of the ratio of arterial oxygen tension (PaO_2) to FiO_2 is currently required to satisfy the hypoxaemia criterion for the diagnosis of ARDS; however, arterial blood gas analysis is invasive and is not available in all settings
- Pulse oximetry is widely used for clinical monitoring and decision making in critically ill patients; it is continuously available, non-invasive, easily interpreted, and easily accessible across care settings
- SpO_2 and related indices such as the SpO_2/FiO_2 ratio have been validated for the clinical diagnosis and management of ARDS; a growing body of evidence also supports the use of pulse oximetry-based measurements in clinical trials and observational studies of ARDS
- Drawbacks of pulse oximetry include reduced accuracy in poor perfusion states and occasional over-estimation of true oxygenation; however, benefits such as earlier recognition of ARDS outweigh these limitations
- Studies are needed to address the possibility of reduced accuracy of pulse oximetry in patients with darker skin pigmentation
- Expanding the use of pulse oximetry to the diagnosis and management of ARDS could help to address underdiagnosis and under-recognition of ARDS, improve understanding of global epidemiology, and facilitate screening for clinical trials

ARDS=acute respiratory distress syndrome. FiO_2=fraction of inspired oxygen. PaO_2=partial pressure of arterial oxygen. SpO_2=pulse-oximetric oxygen saturation.

to expand the definition of ARDS to include patients on high-flow nasal oxygen (HFNO),[19] many of whom do not routinely have arterial lines in place.

Despite the increasing use of pulse-oximetric measurements in both clinical practice and clinical investigation, there is no existing comprehensive review of their use in critical illness. In this Review, we aim to describe the rationale for an expanded use of pulse-oximetric measurements, describe the definitions, derivations, and uses of established and emerging pulse-oximetric indices, address limitations and special considerations of pulse oximetry in characterising hypoxaemia, and outline how these indices could be integrated into future investigations of ARDS and other critical illness syndromes.

Pulse oximetry: accuracy and advantages

The SpO_2 is a reliable indicator of oxygenation status that is widely used in clinical monitoring. The US Food and Drug Administration requires that pulse oximeters approved for clinical use have a root mean square error between SpO_2 and oxygen saturation measured directly in arterial blood (SaO_2) of no larger than 3% for finger oximeters and 3·5% for ear oximeters.[20] Studies of pulse oximetry accuracy in critically ill patients are generally consistent with this guideline.[21–25] One study found that changes in SpO_2 slightly overpredicted changes in SaO_2, but more than 99% of changes in SpO_2 values were within 4% of true changes in SaO_2 values.[26] SpO_2 is also a good predictor of PaO_2 up to saturation values of 97%; above 97% saturation, changes in PaO_2 result in minimal changes in SpO_2 because of the shape of the oxyhaemoglobin dissociation curve (figure 1). Mathematical formulas have been derived with high accuracy for predicting PaO_2 from SpO_2 combined with partial pressure of oxygen in venous blood (PvO_2), partial pressure of carbon dioxide (pCO_2), pH, carboxyhaemoglobin level, and methaemoglobin level,[27] but simple application of the oxyhaemoglobin dissociation curve also performs well when used in undifferentiated critically ill patients.[28] The necessary feature of pulse-oximetric measurements for diagnosis and risk stratification of ARDS is that they correctly classify severity rather than exactly predict PaO_2 from SpO_2 (see below). There are some circumstances or conditions in which SpO_2 might be less accurate, such as in low-perfusion states. Additionally, pulse oximetry cannot identify significant hypercarbia as a cause of hypoxaemia in the absence of other tools such as capnography or an arterial blood gas analysis. When thoughtfully interpreted, however, SpO_2 measurement is a useful screening and diagnostic tool that can be confirmed with or complemented by an arterial blood gas analysis as needed and as available.

Pulse oximetry has the advantages of being continuously measurable, easily interpretable, and available in most settings. Continuous pulse-oximetric monitoring in the

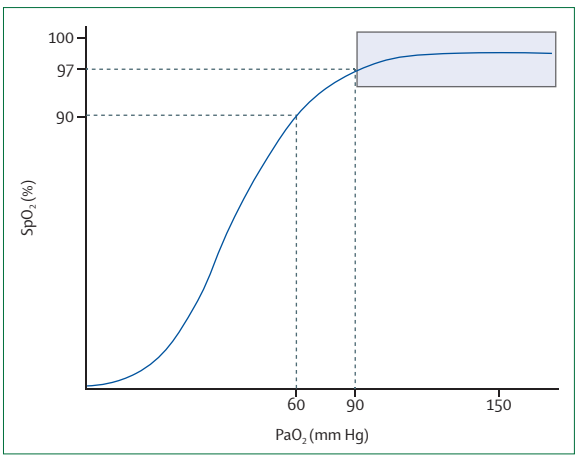

Figure 1: **Oxyhaemoglobin dissociation curve**
An SpO_2 of 90% corresponds to a PaO_2 of approximately 60 mm Hg, and an SpO_2 of 97% corresponds to a PaO_2 of approximately 90 mm Hg. For SpO_2 values higher than 97%, the curve is flat and PaO_2 cannot be reliably estimated from SpO_2. PaO_2=partial pressure of arterial oxygen. SpO_2=pulse-oximetric oxygen saturation.

acute care setting is the widely accepted standard of care where available[29] and is used to guide treatment decisions. By contrast, arterial blood gas measurements capture only a snapshot of the patient's oxygenation status. Furthermore, haemoglobin saturation better reflects some of the physiological derangements of ARDS such as intrapulmonary shunt.[30] This is probably one reason that in some studies, pulse-oximetric indices of hypoxaemia are more strongly associated with patient outcomes than those that rely on arterial blood gas measurements.[9,31,32] Arterial blood gas monitoring is also not performed routinely for all patients with hypoxaemia, and therefore patients who would otherwise meet the criteria for ARDS could be missed if no arterial blood gas measurement is obtained. This selection bias for more severe systemic illness despite similarly severe hypoxaemia among patients with arterial blood gas measurements has been demonstrated in the paediatric literature.[33] The increased opportunity for ARDS diagnosis with continuous monitoring of SpO_2 might be one strategy to help to address the persistent underdiagnosis of ARDS,[34,35] which reduces the implementation of supportive care strategies that are proven to reduce adverse outcomes.[35] Because pulse oximetry is more accessible in resource-constrained settings than arterial blood gas measurements, its recognition as a valid diagnostic tool would also improve global estimates of ARDS epidemiology.[16]

Pulse oximetry also confers virtually no risk compared with the risks of frequent arterial blood sampling or intra-arterial catheter placement. Repeated blood draws can contribute to iatrogenic anaemia,[36,37] especially among critically ill patients who often have impaired haematopoiesis.[38] Frequent blood draws also increase the risk of intravascular thrombosis and catheter failure.[39] Rarely, intra-arterial catheter placement results in serious

	Berlin criteria[4]	Kigali modification[16]
Timing	Within 1 week of a known clinical insult, or new or worsening respiratory symptoms	Within 1 week of a known clinical insult, or new or worsening respiratory symptoms
Oxygenation	PaO_2/FiO_2 ratio ≤300 mm Hg	SpO_2/FiO_2 ratio ≤315
PEEP requirement	At least 5 cm H_2O	No PEEP requirement
Chest imaging	Bilateral opacities on chest radiograph or CT not fully explained by effusions, lobar or lung collapse, or nodules	Bilateral opacities on chest radiograph or thoracic ultrasound not fully explained by effusions, lobar or lung collapse, or nodules
Origin of oedema	Not fully explained by cardiac failure or volume overload (need objective assessment, such as echocardiography, to exclude hydrostatic oedema if no risk factor present)	Not fully explained by cardiac failure or volume overload (need objective assessment, such as echocardiography, to exclude hydrostatic oedema if no risk factor present)

ARDS=acute respiratory distress syndrome. FiO_2=fraction of inspired oxygen. PaO_2=partial pressure of arterial oxygen. PEEP=positive end-expiratory pressure. SpO_2=pulse-oximetric oxygen saturation.

Table 1: **The Berlin diagnostic criteria for ARDS and the Kigali modification**

vascular complications such as permanent arterial occlusion and pseudoaneurysm formation.[40] The placement of an intra-arterial catheter also carries risks of bacterial colonisation and blood stream infection that are comparable to those of a central venous catheter.[41,42] Furthermore, there is no existing evidence that arterial catheters improve clinical outcomes for mechanically ventilated patients.[43] Nevertheless, many patients will have other indications for arterial catheter placement or arterial blood gas monitoring, such as haemodynamic monitoring for shock or severe acid-base disturbances. Among patients for whom the primary indication is hypoxaemia, however, avoiding complications associated with repeated blood draws or arterial catheter placement is a major advantage of relying primarily on pulse oximetry rather than serial arterial blood gas measurements. Reducing the number of arterial blood gas measurements can also reduce the cost of care,[44,45] which benefits both patients and hospital systems.

Pulse-oximetric indices: definitions, derivations, and uses

SpO_2/FiO_2 ratio

The SpO_2/FiO_2 ratio was first described by Rice and colleagues as a valid surrogate for the PaO_2/FiO_2 ratio to quantify hypoxaemia in ARDS non-invasively in adults.[8] In this study, a linear equation derived from patients enrolled in the ARMA trial[46] and validated in patients enrolled in the ALVEOLI trial[47] established the following relationship between the SpO_2/FiO_2 ratio (restricted to SpO_2 ≤97%) and the PaO_2/FiO_2 ratio: $SpO_2/FiO_2 = 64 + 0{\cdot}84\,(PaO_2/FiO_2)$. A threshold SpO_2/FiO_2 ratio of 315 could be substituted for a PaO_2/FiO_2 ratio of 300 mm Hg for the diagnosis of acute lung injury using American European Consensus Conference (AECC) criteria with 91% sensitivity and 56% specificity, and an SpO_2/FiO_2 ratio of 235 could be substituted for a PaO_2/FiO_2 ratio of 200 mm Hg for the diagnosis of ARDS using AECC criteria with 85% sensitivity and 85% specificity.[5,8] Subsequently, the SpO_2/FiO_2 ratio has been widely adopted in paediatric critical care as an alternative diagnostic metric to the PaO_2/FiO_2 ratio for the hypoxaemia criterion in paediatric ARDS (with a different numerical threshold, derived and validated in paediatric populations),[10,15] and the SpO_2/FiO_2 ratio for acute lung injury from the equation proposed by Rice and colleagues was incorporated into the Kigali modification of the Berlin definition of ARDS (table 1).[16] Other studies have also found similar linear relationships between the SpO_2/FiO_2 and PaO_2/FiO_2 ratios,[48,49] and similar cutoffs for the hypoxaemia criteria to identify mild and moderate ARDS.[49,50]

Alternative approaches to the imputation of the PaO_2/FiO_2 ratio from the SpO_2/FiO_2 ratio might be more accurate than a simple linear equation because of the sigmoidal shape of the oxyhaemoglobin dissociation curve (figure 1). A log-linear imputation of the PaO_2/FiO_2 ratio was derived by Pandharipande and colleagues from measurements in a heterogeneous population of patients undergoing general anaesthesia and from patients with ARDS in the ARMA trial database.[14,46] Among all patients in the ARMA database, SpO_2/FiO_2 ratios of 357, 214, and 89 corresponded to the hypoxaemia thresholds for mild (≤300 mm Hg), moderate (≤200 mm Hg), and severe (≤100 mm Hg) ARDS, respectively, by log-linear imputation of the PaO_2/FiO_2 ratio, and this relationship was slightly but not substantially modified when stratified by positive end-expiratory pressure (PEEP).[14] In a retrospective secondary analysis of 1184 patients from the ARDS Network EDEN,[51] EDEN-Omega,[52] and SAILS[53] trials, the PaO_2/FiO_2 ratio derived from a non-linear equation to impute PaO_2[54] was correlated with the measured PaO_2/FiO_2 ratio among all patients (ρ=0·72), with stronger correlation among patients with an SpO_2 of less than 97% (ρ=0·90).[13] ARDS severity was correctly classified in 86% of patients, and severity strata by SpO_2/FiO_2 ratio and by PaO_2/FiO_2 ratio were associated with similar outcomes.[13] A prospective validation of these findings among 703 mechanically ventilated patients in the intensive care unit (ICU) indicated that non-linear imputation was superior to other imputation methods.[12] Sensitivity and specificity for a PaO_2/FiO_2 ratio of 150 mm Hg or less were 0·87 (95% CI 0·83–0·90) and 0·91 (0·88–0·93), respectively, and for a PaO_2/FiO_2 ratio of less than 300 mm Hg were 0·90 (0·88–0·92) and 0·67 (0·61–0·73).[12] The accuracy of non-linear imputation must be weighed against ease of calculation. A simple linear equation might be the easiest way to impute the PaO_2/FiO_2 ratio at the bedside when an arterial blood gas measurement is not available, unless widely accessible clinical decision tools were to be developed—for example, in response to a modification of the current ARDS diagnostic criteria to include the SpO_2/FiO_2 ratio.

Although the SpO_2/FiO_2 ratio has not been formally adopted as a diagnostic criterion for ARDS in the general adult population outside resource-limited settings, numerous studies support the diagnostic

validity of the SpO_2/FiO_2 ratio for meeting the ARDS hypoxaemia criterion. The sensitivity and specificity of the Kigali modification for moderate-to-severe ARDS[16] were tested in the Netherlands, where the data needed to assess the Berlin criteria for ARDS[4] are also readily available. The sensitivity of the Kigali modification was 0·96 (95% CI 0·78–1·00) and the specificity was 0·86 (0·78–0·91); however, specificity improved to 0·93 (0·88–0·97) with the application of more strict ultrasonography criteria, suggesting that the pulse-oximetric criterion was not the primary reason for false-positive diagnoses.[55] An ongoing international observational study to further validate these findings is currently enrolling patients (the NITWA-ARDS Study; NCT03546699).

The SpO_2/FiO_2 ratio also provides similar or even superior prognostic information to the PaO_2/FiO_2 ratio. In a study that directly compared medical ICU patients diagnosed with ARDS by arterial blood gas analysis versus pulse oximetry in a US tertiary care centre, baseline clinical characteristics and clinical outcomes including mortality were similar.[31] Additionally, severe ARDS according to the pulse-oximetric criterion had a stronger association with mortality than severe ARDS diagnosed by arterial blood gas analysis, and diagnostic discordance was rare.[31] Because SpO_2 is continuously available, the SpO_2/FiO_2 ratio can be followed longitudinally more easily than the PaO_2/FiO_2 ratio, increasing available data for prognostication. The SpO_2/FiO_2 ratio time-at-risk profile, or proportion of time that a patient's SpO_2/FiO_2 ratio is less than 150, had slightly better discrimination for mortality than did the lowest PaO_2/FiO_2 ratio as shown by the area under the receiver operating characteristic curve (AUROC 0·81 *vs* 0·78, p<0·001) or the lowest SpO_2/FiO_2 ratio (AUROC 0·79, p<0·001 compared with SpO_2/FiO_2 ratio time-at-risk) in the first 24 h of mechanical ventilation among more than 25 000 mechanically ventilated patients.[56] The SpO_2/FiO_2 ratio can also be substituted for the PaO_2/FiO_2 ratio in the respiratory component of the Sequential Organ Failure Assessment (SOFA) score,[14,57] either by direct substitution or imputation. A large retrospective study of more than 35 000 patients compared linear imputation, non-linear imputation, multiple imputation by chained equations, and direct substitution of the SpO_2/FiO_2 ratio for the PaO_2/FiO_2 ratio versus a missing-as-normal substitution of normal values for calculating the SOFA score.[58] In the overall population, all imputation methods, including direct substitution of the SpO_2/FiO_2 ratio for missing PaO_2/FiO_2 ratios, improved the SOFA score's specificity for mortality compared with the missing-as-normal approach. The improved discrimination for mortality was most pronounced among the subgroup of patients who were missing a PaO_2/FiO_2 ratio at baseline,[58] suggesting that the SpO_2/FiO_2 ratio adds important prognostic information among patients whose clinical picture does not prompt blood gas analysis.

***Panel:* Advantages and disadvantages of SpO_2 measurements in ARDS**

Advantages

- Continuously available
- Highly sensitive for hypoxaemia
- Easily interpretable
- Non-invasive, no risk of procedural complications
- More readily available than PaO_2 in resource-limited settings

Disadvantages

- Measurement error can be increased by conditions commonly seen in the intensive care unit, such as poor perfusion and vasopressor use, severe hypoxaemia, or acidaemia
- Potential for reduced accuracy in patients with darker skin pigmentation
- Potential for misclassification of diagnosis or severity in ARDS

ARDS=acute respiratory distress syndrome. PaO_2=partial pressure of arterial oxygen. SpO_2=pulse-oximetric oxygen saturation.

The SpO_2/FiO_2 ratio has many advantages as a diagnostic tool, but there are some notable limitations (panel), which are discussed in detail in the next section. The SpO_2/FiO_2 ratio cannot be accurately interpreted above saturations of 97%. The use of pulse oximetry also increases the need for caution about the timing of diagnosis (ie, avoiding diagnosis based on isolated or easily corrected low saturation values). Another limitation is possible misclassification of diagnosis or severity (figure 2). This might be acceptable, however, because multiple studies indicate that ARDS diagnosis is likely to be missed or delayed, which has meaningful implications for patient management.[34,35,59–61] Current interventions for ARDS such as low tidal volume ventilation are unlikely to harm a patient with hypoxaemic respiratory failure who is misclassified as having ARDS according to the SpO_2/FiO_2 ratio,[62] and might even provide benefit.[63] In addition to diagnostic misclassification, the SpO_2/FiO_2 ratio might lead to misclassification of ARDS severity; eg, the linear equation yielding an SpO_2/FiO_2 ratio threshold of 235 for ARDS according to AECC criteria misclassified 15% of patients with a PaO_2/FiO_2 ratio of 200 mm Hg or more.[8] However, the SpO_2/FiO_2 ratio does not appear to misclassify patients regarding their clinical outcomes and has been shown in some studies to have better prognostic discrimination for mortality than does the PaO_2/FiO_2 ratio.[9,31] It is therefore unlikely that misclassification of diagnosis or severity with use of the SpO_2/FiO_2 ratio poses a major concern for clinical care, especially when balanced against the possible advantage of facilitating early recognition of ARDS in patients who would otherwise not be diagnosed in a timely manner. As with the PaO_2/FiO_2 ratio, meeting the hypoxaemia threshold

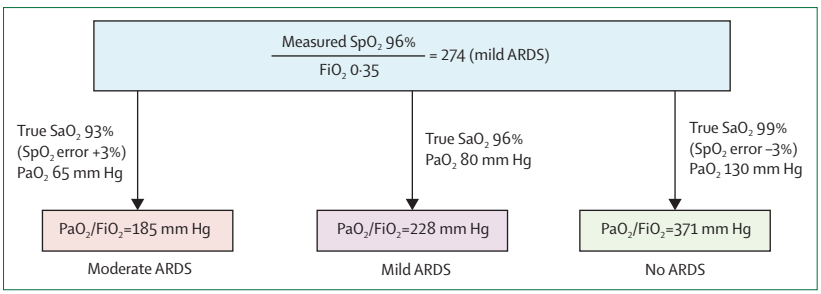

Figure 2: **Examples of how error in SpO_2 measurement could lead to misdiagnosis or misclassification of ARDS**
Pulse oximeters are accurate to approximately 3%. In some cases, measurement error could result in misdiagnosis or misclassification of the severity of hypoxaemia. ARDS=acute respiratory distress syndrome. FiO_2=fraction of inspired oxygen. PaO_2=partial pressure of arterial oxygen. SaO_2=arterial blood oxygen saturation. SpO_2=pulse-oximetric oxygen saturation.

with the SpO_2/FiO_2 ratio is not sufficient for diagnosis of ARDS; other diagnostic criteria still apply, including the presence of a likely predisposing risk factor, radiographic findings, and confirmation that pulmonary oedema is not primarily related to fluid overload or cardiac insufficiency.

Oxygen saturation index

Because the oxygenation index (OI)—(FiO_2×mean airway pressure/PaO_2)×100—incorporates mean airway pressure, some clinicians and investigators consider it to better indicate the severity of respiratory failure than does PaO_2/FiO_2 by accounting for features such as changes in pulmonary compliance and intrapulmonary shunt.[64] In several cohorts, the OI has been shown to be superior to the PaO_2/FiO_2 ratio as an indicator of risk for ARDS mortality.[65,66] The OI also has good discrimination between therapies that are or are not likely to provide benefit,[67] and it is frequently used as a primary or secondary endpoint in ARDS clinical trials.[68] The OSI—(FiO_2×mean airway pressure/SpO_2)×100—which was first described in the paediatric population, is a non-invasive surrogate for the OI.[69] The initial derivation of the OSI was shown to have reasonable sensitivity and specificity for defining acute lung injury and ARDS among children using AECC criteria,[69] and a strong linear relationship between the OI and the OSI has been described in paediatric populations.[10,70,71] The OI or OSI thresholds are used as the hypoxaemia criteria for ARDS among paediatric patients who are invasively mechanically ventilated, in part because mean airway pressure accounts for differences in baseline ventilator management, including PEEP strategy.[15]

Neither the OI nor the OSI has been incorporated into official guidelines as a diagnostic criterion or risk-stratification tool for ARDS in adults, but their prognostic validity has been studied in several settings.[9,72–74] The non-invasive OSI might have more prognostic validity than the arterial blood gas-based OI. In a retrospective observational study of 329 patients with ARDS, the OSI and OI were closely correlated with each other (ρ=0·862, p<0·001), but the OSI was independently associated with mortality when adjusted for age, sex, and severity of illness (adjusted OR for each 1-point increase in OSI 1·228, 95% CI 1·056–1·429, p=0·008), whereas the OI was not.[9] These findings indicate that the OSI is both a good surrogate for the OI and potentially more sensitive for the severity of respiratory failure because it is calculated from the continuously available SpO_2. Other studies have produced similar results. Among 100 patients retrospectively studied in Taiwan, an OSI of 12 or more conferred a statistically significant increased odds of mortality (OR 5·22, 1·31–20·76). A corresponding threshold OI of 16 or more also conferred an increased odds of mortality, but the effect was smaller and did not meet statistical significance (OR 2·92, 0·98–8·68).[75] Another retrospective study of 127 patients with hypoxaemic respiratory failure identified a linear equation for imputing the OI from the OSI:[76] $OI = (0·6075 \times OSI) + 3·45$. The authors also studied the discrimination for ARDS severity thresholds. The OSI had excellent discrimination for a PaO_2/FiO_2 of less than 100 mm Hg (AUROC 0·922) and for a PaO_2/FiO_2 of less than 200 mm Hg (AUROC 0·869), and good discrimination for a PaO_2/FiO_2 of less than 300 mm Hg (AUROC 0·787).[76] The OSI remains relatively understudied in adult ARDS compared with paediatric ARDS for both diagnosis and risk stratification, and the use of non-linear equations to impute PaO_2 for the calculation of the OI from the OSI has not been tested. Further studies of its diagnostic and prognostic validity among adults are required.

ROX index: risk stratification for non-ventilated patients

Expanding the definition of ARDS to include patients on HFNO has recently been proposed.[19] Currently, however, patients on HFNO do not meet ARDS criteria until they progress to non-invasive or invasive mechanical ventilation. One tool for identifying patients at high risk for progression from HFNO to mechanical ventilation is the ROX index, which is calculated as the SpO_2/FiO_2 ratio divided by respiratory rate. A ROX index of more than 4·88 was shown to have good discrimination (AUROC 0·74) for success of HFNO (avoidance of intubation) in the prospective cohort of patients with pneumonia in which it was first described, whereas a ROX index of less than 3·85 was highly predictive of failure.[11] In a subsequent validation cohort, the ROX index was significantly lower at 2 h, 6 h, 12 h, 18 h, and 24 h among patients who eventually required intubation than among those who were successfully managed with HFNO.[77] The AUROC for a ROX index of more than 4·88 for predicting successful management with HFNO was similar in both the prospective validation cohort and the FLORALI cohort, which was used as a second external validation cohort.[77] The ROX index also generally performed better than its individual components for predicting successful use of HFNO, although the SpO_2/FiO_2 ratio also performed well at most timepoints, including before the initiation

of HFNO therapy.[77] The threshold ROX value of more than 4·88 had poor discrimination for predicting HFNO success in immunocompromised patients, indicating that the performance of the ROX index for risk stratification might differ among clinical populations.[78]

The ROX index has been applied during the COVID-19 pandemic for risk stratification and to avoid delayed intubation and possible associated adverse outcomes[79,80] as more patients with what would otherwise qualify as ARDS have been managed using HFNO.[81,82] A Spanish observational study from March to August 2020 found that the baseline ROX index and non-pulmonary SOFA score were the most important variables for predicting progression from HFNO to invasive mechanical ventilation.[83] Other studies support the importance of the ROX index in COVID-19, although some identified a different ROX index cutoff as having optimal sensitivity and specificity for successful use of HFNO[84–89] from that of previous studies of severe pneumonia.[11,77] The ROX index is also predictive of the success of awake prone positioning[90,91] and of non-invasive mechanical ventilation for COVID-19 pneumonia.[92] Differences in the exact ROX index value that predicts successful use of non-invasive respiratory support might be related to different timing of measurements, varying clinician thresholds for intubation during the pandemic, the effect of PEEP for patients on non-invasive mechanical ventilation, and differences in the setting in which patients on HFNO were managed (ICU, wards, or emergency department), as well as demographic and comorbidity differences among patient populations. Each study confirms, however, that the ROX index can be a useful tool for identifying patients who are most likely to be successfully supported using HFNO.

Limitations and special considerations

Generalisability of pulse oximetry-based indices

Limitations of pulse-oximetric tools arise both from the settings and methods used to derive oximetry-based indices and from circumstances that might limit the accuracy of pulse oximetry per se. Owing to the shape of the oxyhaemoglobin dissociation curve, SpO_2 correlates most highly with PaO_2 at SpO_2 values of 97% or less. Thus, the SpO_2/FiO_2 ratio and other oximetric indices are more accurate at saturation levels at or below 97%. Low atmospheric pressure in high-altitude settings also affects the relationship between PaO_2 and SpO_2. The initial derivation and validation of the linear imputation of the PaO_2/FiO_2 ratio from the SpO_2/FiO_2 ratio excluded patients with SpO_2 values of more than 97% and those at more than 1000 m above sea level.[8] The validity of imputing the PaO_2/FiO_2 ratio at higher altitudes using linear, log-linear, or non-linear formulas outside their original derivation and validation cohorts has been demonstrated in at least one study,[93] but applying the linear imputation of the PaO_2/FiO_2 ratio from the SpO_2/FiO_2 ratio to these populations probably requires further validation. The log-linear imputation of the PaO_2/FiO_2 ratio from the SpO_2/FiO_2 ratio included patients both with and without hypoxaemic respiratory failure, with SpO_2 values of up to 98% and PaO_2/FiO_2 ratios of more than 300 mm Hg included in the derivation population.[14] Patients diagnosed with ARDS at high altitude were also included. Although this strengthens the generalisability of the log-linear imputation, the correlation between the SpO_2/FiO_2 and PaO_2/FiO_2 ratios was not as strong in the entire population as it was when limited to patients with ARDS.[14] The non-linear imputation of PaO_2 from SpO_2 in both the retrospective ARDS cohort and the prospective cohort of mechanically ventilated critically ill patients included any SpO_2 value, but accuracy was better among patients with SpO_2 values of less than 97%; imputed values were adjusted for local barometric pressure.[12,13] The OSI has not been studied at SpO_2 values above 97%.[9,15,69] PEEP also slightly modified the relationship between the SpO_2/FiO_2 and PaO_2/FiO_2 ratios in both the linear and log-linear imputations, but the authors in both cases concluded that this was unlikely to substantially affect accuracy.[8,14] There was no relationship between PEEP and imputed PaO_2/FiO_2 using the non-linear imputation method for imputing PaO_2 from SpO_2.[12,13] Taken together, these studies indicate that use of the SpO_2/FiO_2 ratio and the OSI should be limited to SpO_2 levels of 97% or less, when possible, and that the inclusion of PEEP in the imputation of the PaO_2/FiO_2 ratio is not necessary.

Sources of measurement error

The accuracy of pulse-oximetric indices also depends on the measurement error of the pulse oximeter. Carboxyhaemoglobin, methaemoglobin, glycohaemoglobin, sickle cell disease, poor perfusion states, acidaemia, nail polish, and motion artifact can all affect the accuracy of pulse oximetry.[22,94,95] In critically ill patients, acidaemia and poor perfusion states are the most relevant factors. Receiving vasopressors affected the accuracy of the relationship between the PaO_2/FiO_2 and SpO_2/FiO_2 ratios in the retrospective derivation of the non-linear imputation of PaO_2 from SpO_2,[13] but no effect was observed prospectively.[12] Some studies of critically ill patients have found that acidaemia reduces accuracy when estimating SaO_2 from SpO_2,[24,26] whereas others have found no effect.[25] Imputation studies have generally not investigated the effect of acid-base status, however, because of the requirement for blood gas data. Pulse oximeters are also more likely to overestimate saturation in people with darker skin pigmentation, especially at lower saturations.[25,96,97] The effect of skin pigmentation on the relationship between SpO_2/FiO_2 and PaO_2/FiO_2 ratios was specifically studied in the prospective validation of the non-linear imputation of PaO_2 from SpO_2 and found to have no effect,[12] but other studies have not investigated whether skin pigmentation modifies this relationship. Black patients are at higher

	Study type (year or status)	Population and intervention	Use of pulse oximetry
Paediatric studies*			
Paediatric calfactant in acute repiratory distress syndrome[106]	Multicentre, randomised, blinded, placebo-controlled, phase 3 trial (2013)	110 children aged 37 weeks to 18 years with direct ALI or ARDS randomly assigned to intratracheal exogenous surfactant *vs* placebo	Participants could be enrolled with a qualifying SpO_2/FiO_2 ratio of ≤250; secondary outcome of changes in oxygenation included change in SpO_2/FiO_2 ratio for patients enrolled using pulse oximetry
Randomised Evaluation of Sedation Titration for Respiratory Failure (RESTORE)[107]	Multicentre, cluster-randomised, controlled, open-label, phase 3 trial (2015)	2449 children aged 2 weeks to 17 years with acute respiratory failure randomly assigned (by study site) to protocolised sedation *vs* usual care	OSI could be used for a qualifying diagnosis of paediatric ARDS; included patients were considered to be at risk of paediatric ARDS by OI or OSI
Adult studies*			
Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure[108]	Prospective, randomised, crossover study (2003)	72 adults with early ALI or ARDS randomly assigned to a high-PEEP strategy in the ALVEOLI trial; participants received recruitment manoeuvres and sham recruitment manoeuvres on alternate days	Primary outcome of change in SpO_2 during the first 10 min after intervention
A decremental PEEP trial identifies the PEEP level that maintains oxygenation after lung recruitment[109]	Prospective, single-centre clinical trial (2006)	20 adults in a surgical ICU with ALI or ARDS and baseline PEEP ≥8 cm H_2O; participants received up to three lung recruitment manoeuvres followed by a decremental PEEP trial	SpO_2 was used to assess interval response to recruitment manoeuvres before measuring the primary outcome of PaO_2/FiO_2 ratio
Calfactant for Direct Acute Respiratory Distress Syndrome (CARDS)[110]	Multicentre, randomised, blinded, placebo-controlled, phase 3 trial (2015)	317 adults with direct ALI or ARDS randomly assigned to exogenous intratracheal surfactant *vs* placebo	Participants could be enrolled with a qualifying SpO_2/FiO_2 ratio of ≤250; secondary outcome of changes in oxygenation included change in SpO_2/FiO_2 ratio for patients enrolled using pulse oximetry
SB-681323 IV for Subjects at Risk of Acute Lung Injury or ARDS[111]	Multicentre, randomised, double-blind, placebo-controlled, phase 2 trial (2015)	77 adults with severe trauma at risk of ARDS, as determined by injury severity score, randomly assigned to receive dilmapimod *vs* placebo	Secondary outcome of change in SpO_2
Lung Injury Prevention Study With Aspirin (LIPS-A)[112]	Multicentre, randomised, double-blind, placebo-controlled, phase 2 trial (2016)	390 adults admitted through the emergency department at risk of ARDS (lung injury prevention score ≥4) randomly assigned to aspirin *vs* placebo	SpO_2/FiO_2 ratio of <315 was used to screen for development of ARDS (primary outcome), which was confirmed with arterial blood gas
Lung Injury Prevention Study With Budesonide and Beta (LIPS-B)[18]	Multicentre, randomised, double-blind, placebo-controlled, phase 2 trial (2017)	59 adults admitted through the emergency department at risk of ARDS (lung injury prevention score ≥4, requiring supplemental oxygen, and with an ARDS risk factor) randomly assigned to budesonide and fomoterol *vs* placebo	Enrolment criterion of hypoxaemia was based on need for at least 2 L supplemental oxygen to maintain SpO_2 of 94–98%; primary outcome was change in SpO_2/FiO_2 ratio
Reevaluation Of Systemic Early Neuromuscular Blockade (ROSE)[17]	Multicentre, randomised, controlled, open-label, phase 2 trial (2019)	1006 adults with moderate-to-severe ARDS (PaO_2/FiO_2 ratio ≤150 mm Hg) and PEEP ≥8 cm H_2O randomly assigned to early neuromuscular blockade with deep sedation or no neuromuscular blockade with light sedation target	Qualifying PaO_2/FiO_2 ratio for enrolment was imputed from SpO_2 in 9% of patients
Treprostinil Sodium Inhalation for Patients At High Risk for ARDS[113]	Single-centre, randomised, double-blind, placebo-controlled pilot trial (2021)	14 adults with a supplemental oxygen requirement or ≥4 L/min and unilateral or bilateral infiltrates on chest x-ray randomly assigned to inhaled treprostinil *vs* placebo	Patients could be enrolled on the basis of PaO_2 or SpO_2 to define hypoxaemia; primary outcome was change in SpO_2/FiO_2 ratio
Adaptive Support Ventilation in Acute Respiratory Distress Syndrome (NCT03715751)	Single-centre, open-label, crossover study (completed; not yet published)	20 adults with ARDS randomly assigned to adaptive support ventilation *vs* lung protective ventilation	SpO_2 was used to titrate ventilation and included as a secondary outcome
Trial of Therapeutic Hypothermia in Patients With ARDS: Cooling to Help Injured Lungs (CHILL; NCT04545424)	Multicentre, randomised, controlled, open-label, phase 2 trial (recruiting)	340 adults with moderate-to-severe ARDS (PaO_2/FiO_2 ratio ≤200 mm Hg) and PEEP ≥8 cm H_2O randomly assigned to targeted hypothermia or normothermia	Qualifying PaO_2/FiO_2 ratio can be imputed from SpO_2; secondary outcomes include SpO_2 and OSI
Acetaminophen and Ascorbate in Sepsis: Targeted Therapy to Enhance Recovery (ASTER; NCT04291508)	Multicentre, randomised, double-blind, placebo-controlled, interventional platform trial (recruiting)	900 adults with sepsis-induced hypotension or respiratory failure randomly assigned in parallel to acetaminophen, vitamin C, or placebo	ARDS development is a secondary outcome; ARDS can be diagnosed using SpO_2/FiO_2 ratio or PaO_2/FiO_2 ratio

(Table 2 continues on next page)

	Study type (year or status)	Population and intervention	Use of pulse oximetry
(Continued from previous page)			
COVID-19 studies*			
Safety, tolerability, and outcomes of losartan use in patients hospitalized with SARS-CoV-2 infection: a feasibility study[114]	Single-centre, two-cohort feasibility study (2020)	30 adults admitted to hospital with COVID-19-related pneumonia: 14 patients were enrolled prospectively and initiated losartan during hospital stay; 16 patients from a retrospective cohort continued on losartan at home	7-day change in SpO_2/FiO_2 ratio was included as an outcome
Prone positioning in moderate to severe acute respiratory distress syndrome due to COVID-19: a cohort study and analysis of physiology[115]	Single-centre, retrospective cohort study (2021)	261 mechanically ventilated adults with COVID-19: 62 patients proned *vs* 199 controls	Change in OSI on days 1–7 was a secondary outcome
RECOVERY–Respiratory Support: Respiratory Strategies in Patients with Coronavirus COVID-19 – CPAP, High-Flow Nasal Oxygen, and Standard Care (ISRCTN16912075)	Multicentre, adaptive (group-sequential), pragmatic, randomised, controlled, open-label effectiveness trial (completed; not yet published)	4002 adults with COVID-19 and hypoxaemia randomly assigned 1:1:1 to HFNO, CPAP, or standard care	Hypoxaemia inclusion criterion was defined by SpO_2 ≤94% with FiO_2 ≥0·4
Cholecalciferol to Improve the Outcomes of COVID-19 Patients (CARED; NCT04411446)	Multicentre, randomised, double-blind, placebo-controlled, phase 4 trial (completed; not yet published)	218 adults with COVID-19-related pneumonia randomly assigned to single capsule of high-dose vitamin D *vs* placebo	Primary outcome of change in respiratory SOFA score was calculated using SpO_2/FiO_2 ratio rather than PaO_2/FiO_2 ratio
A Multicentre, Single-Treatment Study to Assess the Safety and Tolerability of Lyophilised Lucinactant in Adults With COVID-19 Associated Acute Lung Injury (NCT04389671)	Multicentre, open-label, single-arm, phase 2 trial (recruiting)	20 adults with COVID-19-related ARDS will receive intratracheal exogenous surfactant therapy	Secondary outcomes include SpO_2 and SpO_2/FiO_2 ratio on day 1 after intervention
Lipid Ibuprofen Versus Standard of Care for Acute Hypoxaemic Respiratory Failure Due to COVID-19 (LIBERATE; NCT04334629)	Multicentre, randomised, blinded, controlled, phase 4 trial (recruiting)	230 adults with COVID-19-related hypoxaemic respiratory failure randomly assigned to ibuprofen *vs* standard care	Inclusion criterion for hypoxaemic respiratory failure can be met by SpO_2/FiO_2 ratio of ≤315

ALI=acute lung injury. ALVEOLI=Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury. ARDS=acute respiratory distress syndrome. CPAP=continuous positive airway pressure. FiO_2=fraction of inspired oxygen. HFNO=high-flow nasal oxygen. ICU=intensive care unit. OI=oxygenation index. OSI=oxygen saturation index. PaO_2=partial pressure of arterial oxygen. PEEP=positive end-expiratory pressure. SOFA=Sequential Organ Failure Assessment. SpO_2=ratio of pulse-oximetric oxygen saturation. *Studies listed by trial name or title of published report.

Table 2: **Examples of clinical studies using pulse oximetry in ARDS**

risk of ARDS mortality than are white patients.[98] Although it is possible that misclassification of ARDS severity on the basis of inaccurate pulse oximetry readings in patients with dark skin could contribute to this observed disparity, it seems unlikely that it would have a major effect in view of the findings of the study of non-linear imputation.[12]

If the definition of ARDS is expanded to include patients receiving HFNO or other patients managed on open oxygen delivery systems,[19] the relationship between the SpO_2/FiO_2 and PaO_2/FiO_2 ratios will require further validation in these patient groups, especially because of the challenge of accurately measuring delivered FiO_2 for these devices.

Challenges for implementation

There are additional challenges to the widespread adoption of pulse-oximetric indices. If the SpO_2/FiO_2 ratio is adopted as a diagnostic criterion for hypoxaemia in ARDS, would one imputation formula be appropriate for all settings? If so, which formula should be used? Some interventions are targeted on the basis of severity of hypoxaemia in ARDS, such as prone positioning in patients with a PaO_2/FiO_2 ratio of less than 150 mm Hg,[6] and targeting these interventions to SpO_2/FiO_2 ratios has not been formally studied. There is also still equipoise about whether critically ill patients should be managed with a conservative approach to oxygen therapy (target SpO_2 approximately 90–96%) or a liberal approach (target SpO_2 >96%).[99–101] If the liberal oxygen strategy is shown to be beneficial and is widely adopted, the number of measurements from which the PaO_2/FiO_2 ratio could reliably be imputed will probably be reduced. A retrospective analysis of two large databases of ICU patients in the USA showed that mortality is lowest for patients with SpO_2 readings that are consistently between 94% and 98%, suggesting that calculating the SpO_2/FiO_2 ratio and other metrics at saturation values

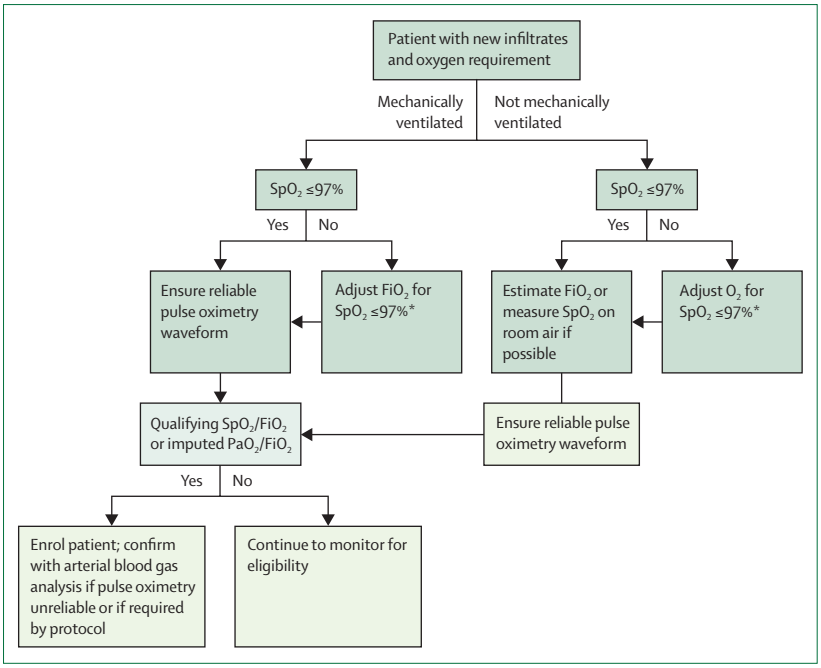

Figure 3: **Example flowchart for enrolment of patients into clinical trials or studies using pulse oximetry**
Pulse-oximetric measurements can be used in studies of both mechanically ventilated patients with ARDS and patients on other modes of supplemental oxygen (eg, patients at risk of ARDS or non-ventilated patients with acute hypoxaemic respiratory failure). Pulse-oximetric indices should not be used if SpO_2 is above 97% because the oxyhaemoglobin dissociation curve is flat above this value. High-quality pulse oximetry measurements should be made when the patient is at rest, at least 10 min after any changes in FiO_2, and when there is a high-quality waveform. FiO_2=fraction of inspired oxygen. PaO_2=partial pressure of arterial oxygen. SpO_2=pulse-oximetric oxygen saturation. *Alternatively, assessment can be made using arterial blood gas.

	Qualifying SpO_2 for a PaO_2/FiO_2 ratio threshold of ≤100 mm Hg	Qualifying SpO_2 for a PaO_2/FiO_2 ratio threshold of ≤150 mm Hg	Qualifying SpO_2 for a PaO_2/FiO_2 ratio threshold of ≤200 mm Hg	Qualifying SpO_2 for a PaO_2/FiO_2 ratio threshold of ≤300 mm Hg
0·30	Ineligible	<81%	<91%	<97%
0·35	Ineligible	<87%	<94%	<97%
0·40	Ineligible	<91%	<96%	<97%
0·45	<81%	<94%	<97%	<97%
0·50	<86%	<95%	<97%	<97%
0·55	<89%	<97%	<97%	<97%
0·60	<91%	<97%	<97%	<97%
0·65	<93%	<97%	<97%	<97%
0·70	<94%	<97%	<97%	<97%
0·75	<95%	<97%	<97%	<97%
0·80	<96%	<97%	<97%	<97%
0·85	<97%	<97%	<97%	<97%
0·90	<97%	<97%	<97%	<97%
0·95	<97%	<97%	<97%	<97%
1·00	<97%	<97%	<97%	<97%

Thresholds are given for FiO_2 values from 0·30 to 1·00, presented in the left-hand column. Reproduced from Brown and colleagues,[33] by permission of the American College of Chest Physicians. FiO_2=fraction of inspired oxygen. PaO_2=partial pressure of arterial oxygen. SpO_2=pulse-oximetric oxygen saturation.

Table 3: **Specific PaO_2/FiO_2 ratio thresholds based on non-linear imputation of PaO_2 from SpO_2, by FiO_2**

below or equal to 97% is safe when SpO_2 is also above 94%.[102]

A current challenge facing the field of ARDS investigation as a whole is the heterogeneity of this clinically defined syndrome, which has been an obstacle to identifying effective therapeutics and treatable phenotypes. Although the use of pulse-oximetric indices could increase this heterogeneity by increasing the number of patients identified with ARDS, there is also an opportunity to identify patients at an earlier stage of their syndrome and to identify additional phenotypes of ARDS. It is important to note that misclassification of ARDS diagnosis or severity potentially introduced by pulse oximetry might affect the conduct of clinical trials by reducing statistical power to detect an effect.[103] In other ways, however, increased and earlier recognition of ARDS through the use of the pulse-oximetric measures for screening[104,105] and diagnosis could be beneficial for the conduct of clinical trials. For example, use of the SpO_2/FiO_2 ratio to increase recognition of ARDS might more accurately reflect background ARDS incidence, increase the number of patients screened for inclusion, improve opportunities for research in resource-limited settings, and better align research populations with clinical practice. In individual cases in whom misclassification is of particular concern—eg, in patients whose SpO_2/FiO_2 ratio is near a threshold value, or in whom a therapeutic intervention could be harmful if severity is misclassified—the diagnosis or severity categorisation could be confirmed with a blood gas measurement as needed and as available, providing that all other diagnostic criteria for ARDS are met. Many clinical trials have already successfully used pulse-oximetric measurements such as the SpO_2/FiO_2 ratio for screening and diagnosis or as outcomes (table 2).[17,18,106–115] An illustration of how the SpO_2/FiO_2 ratio could be used to screen and enrol patients with ARDS into clinical trials is provided in figure 3. Lastly, although pulse oximetry is an excellent tool for expanding the timely diagnosis, management, and study of ARDS and other critical illnesses in resource-variable settings, most pulse-oximetric indices have primarily been studied either in North American and European populations or in settings where resources such as mechanical ventilation and HFNO are readily available. Pulse-oximetric indices require further study in diverse global settings to be truly universally applicable.

The future of pulse oximetry in ARDS

Pulse-oximetric indices have an important role to play in the future of ARDS research and clinical practice. Pulse oximetry is widely used, continuously available, easily interpreted, and requires minimal equipment or expertise. The SpO_2/FiO_2 ratio is already well characterised in ARDS. Although its implementation in some settings might require further study, the SpO_2/FiO_2 ratio has been adopted not only in paediatric and resource-limited

settings, but also in the clinical management of adults in some highly resourced areas. The SpO_2/FiO_2 ratio has been used as both an inclusion criterion and an endpoint in some clinical trials and observational studies, supporting its validity as a tool for future research. The OSI is less well studied in adults but offers promise as an important metric to non-invasively characterise the severity of acute hypoxaemic respiratory failure. The ROX index is useful for risk stratification of patients with hypoxaemic respiratory failure who are not mechanically ventilated and has been increasingly implemented during the COVID-19 pandemic.

We recommend adoption of the SpO_2/FiO_2 ratio as a formal diagnostic alternative to the PaO_2/FiO_2 ratio for the hypoxaemia criterion in adult ARDS. However, in certain instances, such as when the SpO_2/FiO_2 ratio is near a threshold severity value, the accuracy of the pulse oximeter is in doubt, or the SpO_2/FiO_2 ratio and clinical picture seem discordant, a confirmatory arterial blood gas analysis might be needed. For accurate diagnosis and risk stratification, the SpO_2/FiO_2 ratio should be calculated when SpO_2 is 97% or less; consistent messaging and education around this issue is needed. The non-linear imputation formula for the PaO_2/FiO_2 ratio correctly classifies more patients than does linear or log-linear imputation, especially when hypoxaemia is severe, but requires a fairly complex calculation.[54] Clinical decision tools are available, however, that can simplify the application of this equation at the bedside (table 3). A limitation of this formula is that it involves imputation of PaO_2 rather than the PaO_2/FiO_2 ratio directly and, therefore, there is no unique SpO_2/FiO_2 ratio that would always meet the hypoxaemia criterion for ARDS using non-linear imputation. The importance of accurate classification must be weighed against the convenience of a simple linear formula both on an individual patient level and for any changes to the definition of ARDS.

Several areas require additional research, including studies on the relationship between the PaO_2/FiO_2 ratio and the SpO_2/FiO_2 ratio in patients managed with HFNO, further studies of the OSI in adult ARDS, and additional prospective studies of whether skin pigmentation, altitude, or vasopressor use modify the relationship between the PaO_2/FiO_2 and SpO_2/FiO_2 ratios. If the SpO_2/FiO_2 ratio is adopted as an official diagnostic criterion for hypoxaemia in ARDS, prospective studies of the effect of this change on the epidemiology, severity classification, and outcomes of patients with ARDS will be warranted. In summary, pulse oximetry is an indispensable tool as the definition, study, and management of ARDS move forward in the 21st century.

Search strategy and selection criteria

We searched PubMed (MEDLINE) and EMBASE for articles published in English from database inception to Dec 1, 2021, using combinations of the following terms: "acute respiratory distress syndrome", "adult respiratory distress syndrome", "ARDS", "critical illness", "pulse oximetry", "SpO_2", "SpO_2/FiO_2", "oxygenation index", "oxygen saturation index", "OSI", and "ROX index". The abstracts of research and review articles and the references of selected studies were screened, and articles were included on the basis of their relevance to the topics covered in this Review. We also searched ClinicalTrials.gov to identify planned and ongoing trials in acute respiratory distress syndrome or critical illness in adults using pulse-oximetric measurements for inclusion or as endpoints.

Contributors

LBW had the initial idea for the Review and its aims. KDW and LBW did the literature search. KDW drafted the initial manuscript. LBW and MAM critically reviewed and revised the manuscript. KDW created the figures and tables.

Declaration of interests

KDW has received research grant support from the US National Institutes of Health (NIH; 5T32GM008440-24). MAM has received research grant support from the NIH (HL134828, HL126456, HL140026, and 143896), the US Department of Defense, and Roche-Genentech for observational studies on acute respiratory distress syndrome; he reports consultancy fees from Citius Pharmaceuticals, Johnson & Johnson, Gilead Pharmaceuticals, Plant Therapeutics, and Novartis pharmaceuticals, outside of the submitted work. LBW has received research grant support from the NIH (HL103836, HL126176, HL158906) and the US Department of Defense, and grants or contracts from Genentech, Boehringer Ingelheim, and CSL Behring; she reports consultancy fees from Foresee, Merck, Citius Pharmaceuticals, Quark, and Boehringer Ingelheim, outside of the submitted work.

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