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Validation of diagnostic criteria for ARDS in low resource populations

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VALIDATION OF DIAGNOSTIC CRITERIA FOR ARDS IN LOW RESOURCE POPULATIONS

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ABSTRACT

Acute Respiratory Distress Syndrome (ARDS) is a clinical syndrome of multiple etiologies that leads to widespread alveolar inflammation, hyaline membrane formation and noncompliant lungs. ARDS remains underdiagnosed and undertreated with a high mortality rate in high and low income countries. There are limited treatment options for ARDS, including protective lung ventilation, fluid management, prone positioning and ECMO, which may not be used for a patient if they are not diagnosed correctly with ARDS. ARDS is underdiagnosed in low income countries due to the lack of resources, and the resulting lack of access to invasive tools used in the current gold standard diagnostic criteria for ARDS, the Berlin Criteria. To address this issue, Riviello and colleagues introduced the Kigali criteria, that diagnose ARDS using noninvasive tools which are available in low income nations. Vercesi and colleagues examined the Kigali criteria in ICU patients in the Netherlands and found a strong specificity when using stricter Lung Ultrasound criteria. The purpose of this study is to validate the utilization of the Kigali criteria in the early diagnosis of ARDS, with the use of echocardiography, physical exam findings, strict lung ultrasound criteria, and SpO_2/FiO_2 in screening patients on arrival to Emergency Departments and repeatedly during admission to 7 hospitals in the Boston area.

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LIST OF ABBREVIATIONS

AECC ..... American-European Consensus Conference

APACHE ..... Acute Physiology and Chronic Evaluation

APRV ..... Airway pressure release ventilation

ARDS ..... Acute Respiratory Distress Syndrome

ARDS Net ..... National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Trial Network

ASE ..... American Society of Echocardiography

BLUE ..... Bedside Lung Ultrasound in Emergency

BNP ..... B-type natriuretic peptide

BU ..... Boston University

CT ..... Computed tomography

CVC ..... Central Venous Catheter

DAD ..... Diffuse alveolar damage

DAMP ..... Danger Associated Molecular Pattern

EACVI ..... European Association of Cardiovascular Imaging

ECHO ..... Echocardiography

ECMO ..... Extracorporeal membrane oxygenation

ED ..... Emergency Department

EF ..... Ejection fraction

EVLW ..... Extravascular lung water

FACTT trial ..... Comparison of Two Fluid-Management Strategies in Acute Lung Injury

ICU ..... Intensive care unit

IMV ..... Invasive mechanical ventilation

IRB ..... Institutional Review Board

ISO ..... International Standards Organization

LA ..... Left atrium

LUS ..... Lung ultrasound

LV ..... Left ventricle

LVFP ..... Left ventricular filling pressure

MI ..... Myocardial infarction

NIV ..... Noninvasive ventilation

NPV ..... Negative predictive value

NSAID ..... Nonsteroidal anti-inflammatory drugs

PAC ..... Pulmonary Artery Catheter

PAMP ..... Pathogen Associated Molecular Pattern

PCWP ..... Pulmonary Capillary Wedge Pressure

PEEP ..... Positive End-Expiratory Pressure

PPV ..... Positive predictive value

RCT ..... Randomized controlled trial

SOFA ..... Sequential Organ Failure Assessment

TV ..... Tidal volumes

V/Q ..... Ventilation/perfusion

INTRODUCTION

Background

Acute Respiratory Distress Syndrome (ARDS) is a clinical syndrome defined by an acute onset of respiratory distress characterized by diffuse pulmonary infiltrates on imaging, not entirely attributed to left heart failure.[1,2] Over the past 20 years, the epidemiology of ARDS has varied based on the criteria used to define it.[3] Prior to the development of the American-European Consensus Conference (AECC) criteria in 1994, there was no consolidated definition for ARDS. The AECC ARDS criteria provided the first such definition allowing ARDS patients to be diagnosed and, thereby, enabling standardization for clinical trials. However, due to the inability of the AECC ARDS criteria to reliably diagnose ARDS in patients that later exhibited the pathological hallmarks of ARDS upon autopsy, the Berlin definition was introduced in 2012.[2] The Berlin definition attempted to decrease physician subjectivity by standardizing ARDS symptoms, like the timeframe for the acuity of onset, the imaging findings on either chest radiograph or computed tomography (CT), the standard PaO_2/FiO_2 ratios, adding a standard minimum qualifying Positive End-Expiratory Pressure (PEEP) of $5cmH_2O$, and removing of the Pulmonary Capillary Wedge Pressure (PCWP).[2] The PaO_2 value is a measurement of the partial pressure of oxygen in the arterial blood, which is measured directly by arterial sampling. The FiO_2 measurement represents the fraction of oxygen in the inspired air, which is 0.21. PEEP represents the pressure maintained in the lungs after a full expiration. PCWP is an estimate of left atrial pressure, which is measured by a right heart catheter placed in a pulmonary artery. PCWP was used in the AECC criteria to rule out a cardiac etiology

as the cause of pulmonary edema. Since 2012, the Berlin definition has been regarded as the gold standard diagnostic and stratification tool for ARDS and is used for selecting patients for inclusion in ARDS clinical trials.

There is a proposed modified definition for ARDS, the Kigali modification, that uses noninvasive tools, such as ultrasound and echocardiography (ECHO), which could potentially be utilized in resource-constrained locations. The use of ultrasound has transformed the practice of critical care, enabling the clinician to obtain crucial clinical data noninvasively at the patient's bedside. Ultrasound can be used in resource-constrained settings that do not have access to radiology or invasive measurements, such as chest radiography, CT, right heart catheterization and arterial catheters, and, thus, its use would provide a benefit in providing objective measurements to clinicians, allowing them to make informed decisions in clinical management. Lichtenstein and colleagues developed the "Bedside Lung Ultrasound in Emergency" (BLUE) protocol, an algorithm that evaluates lung ultrasound profiles and provides highly accurate data for use in diagnosing an array of pulmonary syndromes.[4] Some recent developments have demonstrated promising results for noninvasive bedside examination of patients, the BLUE protocol, used for diagnosing specific pulmonary syndromes, and the American Society of Echocardiography (ASE) protocol, used to determine left sided filling pressures in the heart. The combination of these protocols may be beneficial in providing early diagnosis of ARDS in resource-constrained populations.[54]

Statement of the Problem

Over the past 20 years, the epidemiology of ARDS has differed based on the location of the study and the criteria used for diagnosis. Incidence has varied from 10.1 to 86.2 cases per 100,000 person-years using the AECC and the Berlin criteria.[6] The global estimation of the current incidence of ARDS is difficult to predict across nations.[7] Many clinical trials take place in well-developed nations that have access to the imaging and invasive measures necessary to determine ARDS using the Berlin definition. Thus, ARDS is largely underrecognized in low-income nations because they lack the resources required to perform diagnostic tests.[8]

In 2014, Riviello and colleagues developed the Kigali criteria, a modified ARDS definition requiring less invasive diagnostic tools, for use in lower income populations. This criteria uses oxygen saturation probes for measuring SpO_2 in place of arterial samples and lung ultrasound in place of CT.[8] SpO_2 is a measurement of blood oxygen saturation, the percent of hemoglobin molecules saturated with oxygen.[9] More specifically, they performed a prospective observational study that incorporated SpO_2/FiO_2 in place of PaO_2/FiO_2, added lung ultrasound to chest radiograph in place of CT, removed a minimum PEEP value, and compared the results to the gold standard, Berlin definition.[8] They found a differing incidence between the Kigali modification and the Berlin criteria due to limited access to invasive tools and chest radiograph in Rwanda.

In 2018, Vercesi and colleagues performed a follow up study, examining the diagnostic accuracy of the Kigali modification compared to the Berlin criteria.[10] In this study, they included analysis of multiple changes to the Kigali criteria compared to the

Berlin criteria.[10] One change applied a stricter lung ultrasound (LUS) criteria that required more lung zones to have imaging findings consistent with ARDS for a positive diagnosis, which improved the diagnostic accuracy of the Kigali criteria.[10]

There are many limitations in the Kigali modification, including the possible inclusion of cardiogenic pulmonary edema. The Kigali criteria requires an objective measurement using echocardiography (ECHO) to rule out hydrostatic edema fully explained by cardiac failure.[8] The Kigali criteria also fails to specify the standards used to rule out cardiac etiology beyond a patient's history of a myocardial infarction (MI) or heart failure in the chart and/or using ECHO to rule out valvular pathology.[8]

Lastly, there is a paucity of research examining the time from a patient's presentation to the emergency department to the diagnosis of ARDS. The timing of ARDS onset from the patient's admission to the hospital floor and the Intensive Care Unit (ICU) has been found to be associated with disease severity and outcome. Late onset of ARDS, generally defined as >48 hours from admission, is associated with a poorer prognosis and greater disease severity than earlier onset.[11] The timing of ARDS onset and therapeutic intervention have become independent prognostic factors in the clinical outcome.[11] Early institution of protective lung ventilation improves the outcome of ARDS and is the cornerstone of therapy.[12,13] Other strategies in lung ventilation, including airway pressure release ventilation (APRV), have been explored in the early management of ARDS[14] with early application of APRV resulting in improved oxygenation, respiratory system compliance, fewer days in the ICU, and lower duration on mechanical ventilation.[12]

With the introduction of the Kigali Modification, which uses noninvasive measurements, ARDS may be diagnosed sooner, allowing for triage to protective ventilation strategies and extracorporeal membrane oxygenation (ECMO). These interventions have proven beneficial if introduced early in the disease course.[15] The modified Kigali protocol may also be applicable in low-income areas in which patients have limited treatment options, enabling them to be screened, diagnosed and transported to an institution with mechanical ventilation earlier in the disease course.

Hypothesis

The use of the modified Kigali definition incorporating tissue doppler and lung ultrasound will lead to an earlier diagnosis of ARDS when compared to the Berlin criteria.

Objectives and specific aims

Because evidence suggests patients benefit from earlier administration of protective lung ventilation strategies and ARDS remains largely underdiagnosed in resource-constrained settings, the objective of this study is to evaluate the time to diagnosis and the diagnostic accuracy of the modified Kigali definition when compared to the Berlin Criteria. Specific aims include:

- To compare the time to diagnosis of ARDS with the modified Kigali criteria with the gold standard Berlin definition
- To determine the diagnostic accuracy of the modified Kigali criteria compared to the Berlin definition incorporating tissue doppler and strict LUS criteria

REVIEW OF THE LITERATURE

Overview

Pathophysiology of acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is clinically defined as a syndrome consisting of multiple etiologies that manifest as an acute inflammatory lung injury, which causes increased pulmonary vascular permeability.[1] Increased permeability leads to increased flooding of the interstitial and alveolar spaces, loss of aerated lung tissue, and Ventilation/Perfusion (V/Q) mismatch reflected by systemic hypoxemia.[2]

Over the past 50 years, progress has been made in understanding the pathophysiological processes underlying this clinical syndrome in animal and human studies. The pathophysiology of ARDS is divided into 3 phases: (1) Exudative; (2) Proliferative; and (3) Fibrotic.[1]

Exudative Phase

The exudative phase is characterized by initial acute lung injury followed by the influx of protein concentrated fluid into the intra-alveolar spaces within the lung, and the interstitial space between the alveoli and microvasculature.[2]

The first steps in the exudative phase often begin within 24 hours of the initial lung injury.[16] The source of injury may be either from a direct source (i.e., direct extension from the lung, such as pneumonia) or from an indirect source (i.e., extension from a systemic source, such as sepsis or a burn injury).[16] Injury can lead to the destruction of susceptible tissues and zones in the lungs, including the alveolar epithelial tissue, the endothelial membrane, and the microvascular tissue that delivers oxygen to the

lungs.[16] Damage to any of these tissues leads to cell membrane disruption shown by the local increase of intracellular markers, i.e., DNA and RNA, that are collectively referred to as Danger Associated Molecular Patterns (DAMPs).[16] If the source of injury is infectious, there will likely be an increased presence of foreign pathogen markers, such as Pathogen Associated Molecular Patterns (PAMPs) that are specific to different bacterial pathogens.[16] The local increases in PAMPs and DAMPs activate the innate immune system, including alveolar macrophages in the lung and the complement cascade in the systemic circulation.[16,17] Activation of the alveolar macrophages transforms their function to an M1 activation state, a hyperinflammatory state characterized by the release of proinflammatory cytokines.[16] This exacerbates the diffuse alveolar inflammation, leading to the recruitment of inflammatory cells, including neutrophils.[16]

Neutrophils release pro-inflammatory mediators that worsen local destruction of the alveolar epithelial-endothelial barrier, the barrier between the lungs and the microvasculature.[16,17,18] The localized proliferation of the inflammatory mediators involved in this process ultimately leads to the breakdown of this barrier, which allows the escape of proteinaceous fluid into the intra-alveolar and interstitial spaces.[16,17]

Epithelial and endothelial cell expression of TNFa, a protein involved in inflammation, leads to the development of proteinaceous hyaline membranes, a pathological hallmark of ARDS, first described by Katzenstein as diffuse alveolar damage (DAD).[19] DAD is characterized by injury to the barrier between the alveoli and the vasculature, increased fluid in the intra-alveolar space, and the presence of protein concentrated extravasate, hyaline membranes.[19]

Proliferative Phase

The proliferative phase begins within 3 days of the initial injury and marks the beginning of the reparative process. The objective of this phase focuses on lung restoration and recovery.[1] It is manifested by the appearance of cells involved in the reparative process, including fibroblasts, fibrocytes, myofibroblasts, and pluripotent mesenchymal progenitor cells that all function to rebuild the basement membrane.[18] During this time, the alveolar macrophages transform into a reparative M2 state to aid in the clearance of inflammatory debris.[17] Additionally, Type II cells differentiate into Type I cells to restore tight junctions and, subsequently, decrease the extravasation of proteinaceous fluid into the lung.[17] At this time, Type II cells restore the synthesis of surfactant, a lipoprotein complex that aids in lung function and compliance.[1]

Fibrotic Phase

The fibrotic phase occurs in the subset of patients with the most severe initial alveolar membrane damage.[1] The body's inability to repair the excessive damage in the lung leads to an elevated, robust response during the fibroproliferative phase, causing a profibrotic shift that leads to long term fibrosis.[16,18] These patients are known to have an increased duration of mechanical ventilation and higher mortality.[1]

Epidemiology/Incidence

Through the advancement of critical care interventions and the incorporation of protective lung ventilation, the estimated incidence and mortality of ARDS have decreased in the United States over the past 20 years.[3] In addition to the advancement of

critical care interventions that allow better treatment of the underlying conditions causing ARDS, the decrease in mortality is largely attributed to the protective lung ventilation strategy made possible by the standardization of its definition in clinical trials.[3]

The global impact and incidence of ARDS is difficult to estimate with the bulk of epidemiological studies conducted predominating in developed countries. Even in developed nations, the estimates for incidence have varied from 10.1 to 86.2 cases per 100,000 person-years over the past 20 years due to differences in the AECC and the Berlin criteria.[6,20] In the most recent large international epidemiological study (LUNGSAFE trial), 29,144 patients from 459 ICUs from 50 countries were examined and it was found that ARDS accounted for 10.4% of ICU admissions with 23.4% of patients requiring mechanical ventilation.[21] Also, the hospital mortality rate was 34.9%, 40.3%, and 46.1% for mild, moderate, and severe ARDS, respectively. Additionally, it was found that, despite access to resources, ARDS remained underdiagnosed and undertreated with clinician recognition ranging from 51.3% for mild cases to 78.5% in severe cases with underutilization of the lung protective ventilation strategy.[21]

In resource-constrained settings, which have limited access to mechanical ventilators and invasive technology to measure PCWPs and PaO_2/FiO_2 ratios, ARDS is likely underdiagnosed due to the inability to measure these parameters.[1,20] For example, in a study examining the impact of ARDS in Rwanda, no cases of ARDS were diagnosed, probably due to the limited resources leading to an inability to apply the Berlin definition. However, 4 cases per 100,000 person-years were diagnosed with a 50% mortality rate using the Kigali modification.[8]

Etiologies

Because ARDS is such a heterogenous disease, there are multiple etiologies that can be classified as: (1) Direct (local) and (2) Indirect (systemic).[1] In recent epidemiological studies, pneumonia, aspiration of gastric contents, and sepsis accounted for 85% of the cases of ARDS[1], however, etiologies vary based on global region. An observational prospective study in India found the main etiologies to be malaria (27.6%), leptospirosis (20.7%), undiagnosed fever (27.6%), and pneumonia (13.8%), which is dissimilar to the United States.[22]

Diagnosis

Historically, the term "acute respiratory distress syndrome" was first coined by Ashbaugh and colleagues.[23] They recognized a clinical parallel between the signs and symptoms of the 12 patients they were treating and neonatal respiratory distress syndrome.[23,24] They noted decreased lung compliance, tachypnea, a large alveolar-arterial oxygen tension difference, radiological changes, and, eventually, changes in autopsy findings showing heavy lungs, alveolar debris, and hyaline membrane formation.[3,19] These findings were later defined as diffuse alveolar damage (DAD), the pathological hallmark of this syndrome described by Katzenstein.[3,19]

For more than 20 years, clinicians lacked gold-standard criteria to diagnose ARDS premortem, leaving the epidemiology, incidence, mortality and incorporation of treatment strategies from randomized controlled trials and observational studies difficult to gauge and translate into clinical practice. For example, mortality rates ranged from 10

to 90% over the past 20 years, making it difficult for clinicians to estimate prognosis with a given clinical presentation.[25] In an attempt to stratify patients based on severity of parenchymal lung injury, Murray and colleagues proposed the incorporation of the lung injury score.[26] The lung injury score functioned as a stratification tool and included PEEP, respiratory system compliance, degree of hypoxemia measured by PaO_2/FiO_2 ratios, and chest radiograph to subcategorize patients based on severity of lung injury for the inclusion in clinical trials.[26] In 1994, the American Thoracic Society and European Society of Intensive Care Medicine created the first uniform definition of ARDS, the AECC criteria, standardizing the diagnosis of ARDS that would ultimately become the foundation for the inclusion criteria in epidemiological and therapeutic intervention studies in subsequent years.[3]

The AECC criteria consisted of 4 categories: timing, hypoxemia, imaging and cardiac exclusion (Table 1).[27] The AECC criteria categorized severity of lung injury based on degree of hypoxemia, distinguishing ARDS with a $PaO_2/FiO_2 \leq 200mmHg$, from Acute Lung Injury (ALI) that had a similar underlying pathophysiology but less severe hypoxemia, 200mmHg<PaO2/FiO2 ≤300mmHg.[27]

Table 1. AECC Criteria used to Diagnose ARDS Introduced in 1994

Timing	Acute and sudden onset
Hypoxemia	ALI: >200mmHg PaO_2/FiO_2 ≤300 mmHg ARDS: PaO_2/FiO_2 ≤200mmHg (regardless of PEEP)
Imaging	Diffuse bilateral infiltrates on chest radiograph
Cardiac Exclusion	Absence of left atrial hypertension, PCWP ≤18mmHg when measured or no clinical evidence of left heart failure

ALI: Acute Lung Injury
ARDS: Acute Respiratory Distress Syndrome
PEEP: Pulmonary End Expiratory Pressure
PCWP: Pulmonary Capillary Wedge Pressure

Although the AECC criteria condensed the constellation of clinical, radiological, and physical abnormalities into a single definition for ARDS, over time, its diagnostic accuracy was questioned. Criticisms of the criteria included insufficient validity and reliability and an inability to segregate patients based on severity of illness into more homogenous groups for entrance into studies.[28] For instance, the AECC criteria lacked a specific timeframe for the onset of symptoms, leaving clinicians to set deadlines based on personal discretion.[3] The oxygenation status was suboptimal in differentiating patients based on severity of lung injury, leading to clinical variation within subgroups submitted for trials.[2] The difference in titles based on hypoxemia, i.e., ALI vs ARDS, led to the inaccurate perception that they were completely separate diagnoses despite their common

underlying pathophysiology.[28] The incorporation of PEEP was considered but, ultimately, avoided due to varying physician practice patterns and clinical settings without access to mechanical ventilation, which would contribute to inaccurate classification.[27] For example, it was noted that, in severe cases of ARDS, mechanical ventilation may not be utilized based on the patient's wishes or the physician's opinion that it would be futile, therefore, underestimating the severity of lung injury in these patients.[27]

The imaging criteria in the AECC definition also lacked explicit clarity on the requirements for a positive finding.[28] Chest radiographs, the imaging modality specified in the definition, have demonstrated a wide interobserver variability and lack of sensitivity, requiring extravascular lung water (EVLW), a marker of pulmonary edema, to be at least 35% above normal for recognition.[29,30,31] Lichtenstein and colleagues examined chest radiograph diagnostic accuracy in comparison to auscultation and lung ultrasound and found the diagnostic accuracy of chest radiograph for pleural effusion (47%), alveolar consolidation (75%), and alveolar interstitial syndrome (72%) was lower than that of ultrasound at 93%, 97%, and 95%, respectively.[32]

The presence of PCWP ≤18mmHg in the criteria for exclusion of cardiac etiology was later questioned. PCWP can fluctuate with fluid resuscitation and can remain high, above 18mmHg, in the absence of heart failure.[33] Frequent oscillation of PCWP values paired with high interobserver variability in interpretation of tracings, no benefit in mortality and increased catheter related complications using pulmonary artery catheter (PAC)-guided therapy compared to the use of central venous catheter (CVC)-guided therapy led to the removal of this mandate in the criteria.[34,35,34]

The AECC criteria demonstrated weak diagnostic accuracy on autopsy when compared to the gold standard pathological hallmark of ARDS, DAD. On autopsy, DAD was documented in only 30.4% of those who met the AECC criteria and only 47.6% of patients with DAD had a diagnosis of ARDS. From this study, the sensitivity and specificity of the AECC criteria were found to be 0.83 and 0.51, respectively.[36] Another study comparing the AECC criteria to autopsy had similar findings with a sensitivity and specificity of 0.71 and 0.67, respectively, and a PPV of 50% and NPV of 83%.[37]

The Berlin definition was created in 2012 to standardize the definition of ARDS with improved reliability and validity.[2] The Berlin definition clarified the existing criteria, removed unnecessary measurements, and retained a compatible definition to continue incorporating the results of previous clinical trials using the AECC criteria.[28] The Berlin definition retained the original four categories with minor changes (Table 2).

Table 2. The Berlin Definition Criteria to Diagnose ARDS Introduced in 2012

Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms [2]
Chest Imaging	Bilateral opacities on chest radiograph or CT not fully explained by effusions, lobar lung collapse, or nodules[2]
Origin of Edema	Not fully explained by cardiac failure or fluid overload with objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present [2]
Oxygenation	Mild: 200mmHg PaO_2/FiO_2 <300mmHg with PEEP or CPAP ≥ 5 cm H_2O Moderate: 100mmHg < PaO_2/FiO_2 < 200 mmHg with PEEP or CPAP ≥5cm H_2O Severe: PaO_2/FiO_2 < 100 mmHg with PEEP or CPAP ≥5cm H_2O[2]

The Berlin criteria established a definitive time frame for the onset of ARDS, provided a more explicit definition of bilateral opacities on imaging, and incorporated the use of CT.[2] The use of CT had a strong association with the detection of EVLW, a marker of pulmonary edema, when compared to the gold standard gravimetric measurement in sheep studies and the gold standard in vivo technique using thermodilution.[38,39,40]

The Berlin criteria also removed PCWP to rule out heart failure due to decreasing use of the right heart catheterization after a study found limited reliability, benefit, and increased mortality in the setting of diagnosing ARDS.[34,35,40] They incorporated the use of PEEP, believing the pros of improving Ventilation/Perfusion (V/Q) mismatching and

intrapulmonary shunt fraction [41] outweighed the cons of underdiagnosis in resource-constrained settings with limited access to mechanical ventilators.[27] Since its introduction, the Berlin diagnostic accuracy has also been questioned. Autopsy findings demonstrated a sensitivity of 89% and specificity of 63% with DAD found only in 45% of patients diagnosed with ARDS, comparable to the autopsy findings for AECC.[42,36,37] The relative inaccuracy of the Berlin definition compared to the pathologic hallmark, DAD, suggests a need for a new definition with improved diagnostic accuracy.

Treatment

Supportive therapy and correction of the underlying precipitants of ARDS are the cornerstones for management with strategies including: (1) Protective Lung Ventilation using lower Tidal Volumes (TV); (2) Optimal PEEP management; (3) Optimal PEEP Using Esophageal Probe; (4) Prone positioning; and (5) Fluid management.[43]

Protective Lung Ventilation

Supportive therapy focuses on appropriate management of the underlying condition and prevention of the propagation of lung injury. The only therapy with proven benefit across all severities of ARDS is the protective lung ventilation strategy.[1] The ARDSnet ARMA trial, which compared higher to lower tidal volume ventilation strategies, demonstrated an improvement in mortality.[44] This trial marked the importance of iatrogenic ventilator induced lung injury in patients with ARDS who are particularly susceptible to regional overdistension.[45] The lung protective ventilation strategy results in the reduction in a number of mechanisms believed to cause lung injury, including: (1)

volutrauma, lung injury associated with high volume and lung stretching; [46] (2) atelectrauma, lung injury associated with repetitive opening and closing of alveoli;[47,48] and (3) biotrauma, the release of proinflammatory mediators with the potential to initiate and propagate local or systemic inflammation that can lead to pulmonary fibrosis.[49,50]

The American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine conducted systematic reviews and meta analyses on ARDS management strategies and published evidence-based clinical guidelines for the management of ARDS published in May 2017.[51] There was agreement for clinical therapy across all ARDS groups with a low tidal volume (TV) (4-8mL/kg) based on predicted body weight and lower inspiratory pressures (plateau pressure <30cm H_2O).[51] These recommendations were established from the ARDSnet ARMA trial published in 2000 (ARMA trial) comparing the previously used 12 mL/kg TV to 6 mL/kg TV, which found a reduction in absolute mortality (39.8% vs. 31.0% p= 0.007).[44] As the cornerstone of management for patients with all severities of ARDS, it is crucial to be able to implement this management therapy early in the course of the disease.

Optimal PEEP Management

Based on the Berlin criteria, a minimum PEEP of 5cmH_2O is required for the diagnosis of ARDS. PEEP has been found to have a considerable effect on PaO_2/FiO_2 ratios and V/Q mismatch.[41] A systematic meta-analysis in 2010 using the data from three trials (ALVEOLI, LOVS, EXPRESS) comparing high and low PEEPs with lower TVs found that those who met the criteria for ARDS with a higher PEEP had a decreased risk of in-hospital mortality (34.1% vs 39.1% p=0.049).[52] Therefore, optimal PEEP setting in

the management of ARDS can be related to clinical outcome, although this belief is controversial and the implementation of PEEP is not universally predictable across all patients and severities.[27]

Optimal PEEP Using Esophageal Probe

The variations in intrapleural pressures, fluctuating with a patient's illness severity, body habitus, and intrabdominal pressures, spurred a trial to estimate the patient's lung compliance using their intrapleural and transpulmonary pressure gathered from esophageal manometry.[53,54,55] Using esophageal manometry, a probe was placed in the esophagus to measure intrapleural pressure and adjust the PEEP accordingly.[54,53,55] Although there was a slight trend towards a decreased mortality rate, this difference was not significant.[1] In the esophageal manometry group, the oxygenation and respiratory system compliance improved, maintaining the mean transpulmonary end expiratory pressure above zero, minimizing alveolar collapse.[55] A larger randomized controlled trial RCT using esophageal manometry is currently underway.[56]

Prone Positioning

In a multicenter prospective RCT, patients with moderately severe to severe ARDS (defined as: PaO_2/FiO_2 <150mmHg , $FiO_2 \geq 0.6$, PEEP $\geq 5cmH_2O$ and TV close to 6mL/kg predicted body weight) had a significant decrease in 28 and 90 day mortality when placed in a prone position for at least 16 consecutive hours.[57] Currently, recommendations are for patients with severe ARDS to be placed in the prone position for 12 hours a day.[51] The function of prone positioning is to improve the V/Q mismatching and shunt perfusion, reallocating blood away from less ventilated regions,[58]

which has demonstrated improved oxygenation and lung compliance.[59] Prone positioning, although not tested in low-income populations, offers a feasible treatment strategy in locations with limited access to resources.

Fluid Management

In 2006, ARDSnet performed a study examining optimal fluid management in patients with ARDS, called the Comparison of Two Fluid-Management Strategies in Acute Lung Injury (FACTT trial).[60] In the FACTT trial, 1,000 patients with acute lung injury were stratified to liberal and conservative fluid management protocols for seven days.[60] Although there was not a significant difference in mortality, the patients who underwent the conservative fluid protocol showed an improvement in their lung injury score and oxygenation index, an increase in ventilator-free days, and decreased number of days spent in the ICU.[60]

In an attempt to further stratify ARDS patients, retrospective data gathered from the 2006 FACTT trial identified subphenotypes bringing more homogeneity to subgroups. A hyperinflammatory subphenotype, "Phenotype 2", was identified.[61] It was associated with increased mortality, sepsis, vasopressor use, lower serum bicarbonate, and higher inflammatory markers, such as IL-6, IL-8, and TNFa, compared to "Phenotype 1".[61] A difference in mortality was found based on a given treatment strategy between the two groups when comparing high to low PEEP and conservative to liberal fluid management.[61] An improved response was found for liberal fluid management in Phenotype 1 (mortality 18% in fluid-liberal vs. 26% in fluid-conservative). In contrast, the investigators found that conservative fluid management in Phenotype 2 resulted in

improved mortality (mortality 40% in fluid-conservative vs. 50% in fluid-liberal).[62] Therefore, modified criteria allowing patients in low-income populations to be placed on the ARDS spectrum could enable these patients to have access to the optimal fluid management appropriate with the identification of these subphenotypes.

Pharmacologic

With the high mortality rate with ARDS, many drug therapies have been tested with no significant reduction in mortality or delayed progression of disease course. Therapies incorporated into clinical trials include inhaled nitric oxide, glucocorticoids, ketoconazole, surfactant replacement, statin, albuterol, antioxidants, anticoagulation, nonsteroidal anti-inflammatory drugs (NSAIDS), and nebulized heparin.[63,64,65,66,67,68] None of these drug therapies have shown a benefit in mortality or course progression in the treatment of ARDS.[68] Currently, there are new trials underway examining the use of mesenchymal stem cells as therapy for ARDS.[69,70]

Current Research on ARDS

The most recent large, international epidemiological study, the LUNGSAFE trial examined 29,144 patients in participating ICUs and determined ARDS represented 10.4% of all ICU admissions and 23.4% of patients on mechanical ventilation.[21] However, while the study examined 459 ICUs in 50 countries, the results were skewed towards high and upper middle income countries with none of the countries involved classified as low-income countries based on the World Bank Classification.[71,21] The prevalence and impact of ARDS in low-income and resource-constrained settings remains difficult to

estimate. The lack of knowledge regarding the incidence and mortality of ARDS in low-income settings suggests a need for modified criteria that can assess the overall impact of this syndrome in these settings. Limited access to resources contributes to the lack of knowledge regarding the global burden of critical illness, as it makes it difficult to conduct the appropriate tests and contributes to a higher short term mortality, leaving a smaller time frame to estimate the true prevalence of the disease.[72]

Epidemiology of ARDS in Developed Countries

In the studies conducted in the developed world over the past 20 years, there have been large discrepancies in the incidence of ARDS reported in varying ICUs. All of the studies required patients to be in the ICU and only one Scandinavian study [73] did not require intubation, reducing the generalizability of this data to resource poor countries with limited access to ICU beds and mechanical ventilation. Recent epidemiological studies estimated the prevalence of ARDS to be between 10 to 86.2 cases per 100,000 person-years.[20] Proposed etiologies of this variation include: ICU bed availability [74]; number of study sites, e.g., single center studies, which suggests differences in population risk factors; characteristics in different populations; seasonal variation; variation in inclusion/exclusion criteria (one study included patients with comorbidities, another included patients with $FiO_2 \geq 40\%$ by mask without invasive ventilation); interobserver variability in radiographic interpretations; inaccurate administrative coding; ventilatory management; variations in treated incidence; and true decreasing incidence of ARDS from improvements in critical care.[20,75,76,77,74]

Treated Incidence

The concept of treated incidence was first applied in examining the epidemiology of severe sepsis across ICUs. The theory of treated incidence can be applied to the epidemiology of other critical illnesses, including ARDS. The incidence of ARDS is a measure of those treated for it, which can vary based on ICU bed availability, ICU resources, and management of predisposing conditions and risk factors.[74] All of the epidemiological studies using the AECC or Berlin criteria have been reported only for ICU patients and, therefore, ICU bed availability has a large impact on the measured incidence of ARDS, regardless of the patient's clinical status. A study in Uganda examining the national ICU bed capacity demonstrated hospital capacity ranged from 2 to 6 beds in 9 hospitals and only 33 adult ICU beds were capable of providing mechanical ventilation in the entire country.[78]

With the etiologies for ARDS differing based on global region, it may be difficult to extrapolate findings across nations. A study in India found the etiologies of ARDS to be malaria (27.6%), leptospirosis (20.7%), undiagnosed fever (27.6%), and pneumonia (13.8%), which differs from the results of a US study in which the etiologies were severe sepsis with suspected pulmonary etiology (46%) and severe sepsis with suspected non-pulmonary etiology (33%).[22,75] With the differing etiologies based on global region, current clinical trials have examined the success of specific treatment strategies in only a subset of patients whose etiologies of ARDS reflected the higher income nations. This

highlights the need for the inclusion of all patients with ARDS in clinical trials, regardless of global region, as varying etiologies may contribute to different outcomes.

The Global Burden of Disease study analyzed data gathered between 1980 and 2010. It examined the global distribution and burden of various diseases, health risk factors, and injuries worldwide. Although it estimated the incidence of various high yield diseases, it failed to estimate the prevalence of ARDS due to the inability of the syndrome to fit into only one of the categories used in the study: 1) Communicable, neonatal, maternal, nutritional disorders; 2) Noncommunicable; and 3) Injuries.[79,20]

Kigali Modification Study in Rwanda

To bridge the gap between the unknown ARDS epidemiology in low-income countries and limited access to resources, Riviello and colleagues examined the incidence of ARDS using the Kigali modification, criteria based on the Berlin definition that can be applied in resource poor settings (Table 3). The study examined the incidence of ARDS using the Kigali modification compared to using the Berlin definition at the University Teaching Hospital in Kigali, Rwanda.[8] The author highlighted an inability to diagnose ARDS based on the Berlin criteria due to limited access to invasive interventions, particularly CT scanning, chest radiography, arterial measurements for oxygenation, and mechanical ventilation.

Revisions Introduced in the Kigali Modification

The changes the Kigali modification introduces are the use of $SpO_2/FiO_2 \leq$ 315mmHg in place of PaO_2/FiO_2 ratios, the use of lung ultrasound instead of CT in the diagnosis of bilateral opacities, and the removal of the PEEP requirement (Table 3).[8]

Table 3 Berlin Definition vs. Kigali Modification

	Berlin Criteria	Kigali Modification
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms[2]	Within 1 week of a known clinical insult or new or worsening respiratory symptoms[8]
Chest Imaging	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules by chest radiograph or CT[2]	Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules by chest radiograph or lung ultrasound[8]
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload (requires objective assessment e.g. echocardiogram to exclude hydrostatic edema if no risk factor present) [2]	Respiratory failure not fully explained by cardiac failure or fluid overload (requires objective assessment e.g. echocardiogram to exclude hydrostatic edema if no risk factor present) [8]
Oxygenation	• Mild: 200mmHg< PaO_2/FiO_2 <300mmHg • Moderate: 100mmHg < PaO_2/FiO_2 <200 mmHg	$SpO_2/FiO_2 \leq 315$ [8]

	• Severe: PaO_2/FiO_2 <100mmHg[2]	
PEEP requirement	Minimum 5 cmH_2O PEEP required by invasive ventilation (noninvasive acceptable for mild ARDS)[2]	No PEEP requirement consistent with AECC definition[8]

ARDS: Acute Respiratory Distress Syndrome
CT: Computed Tomography
PEEP: Positive End-Expiratory Pressure
AECC: American-European Consensus Conference

Evidence of Support of Revisions in the Kigali Modification

Oxygenation

Oxygenation measurements using SpO_2/FiO_2 have demonstrated significant correlation to P_aO_2/FiO_2 values and have been a validated replacement for PaO_2 values.[80] Rice et al demonstrated that the SpO_2/FiO_2 value of 235 resulted in an 85% sensitivity and specificity for P_aO_2/FiO_2 ratio of 200 and the SpO_2/FiO_2 value of 315 had a sensitivity and specificity of 91% and 56%, respectively, for a P_aO_2/FiO_2 ratio of 300.[80] Follow up studies further validated this method by showing similar outcome predictions when using the SpO_2/FiO_2 ratio compared to the P_aO_2/FiO_2 ratios in the daily monitoring of pulmonary parameters of Sequential Organ Failure Assessment (SOFA) scores.[81]

Lung Ultrasound

The use of noninvasive bedside lung ultrasound has shown promise in assisting in the diagnosis of ARDS. Using lung ultrasound, ARDS presents with characteristic lung

profiles defined by Lichtenstein and colleagues.[82,4] It has demonstrated a strong diagnostic accuracy with 93%, 97%, and 95% for pleural effusion, alveolar consolidation and alveolar-interstitial syndrome respectively, a promising improvement from chest radiography and auscultation.[32] In 2008, Lichtenstein and colleagues developed different characteristic lung profiles for various pulmonary pathologies and examined the use of lung ultrasound in aiding in the diagnosis of ARDS.[4] Lung ultrasound had a strong diagnostic accuracy with 97% sensitivity and 95% specificity using the lung profiles associated with various pulmonary pathologies.[4] The BLUE protocol was developed as a stepwise algorithm that could be used bedside to examine the pulmonary function of a given patient.[4] It examines 12 zones on the chest, evaluating the presence or absence of A or B lines, lung sliding, alveolar consolidation and/or pleural effusion.[4] The findings are categorized into different lung profiles. ARDS is associated with multiple profiles.[4]

One study demonstrated promising findings in using lung ultrasound to examine extravascular lung water (EVLW), the fluid extravasated out of the pulmonary vasculature referred to as pulmonary edema, an independent risk factor for ARDS.[83]

Bass and colleagues compared the use of lung ultrasound combined with pulse oximetry (SpO_2) to the use of chest radiography combined with arterial blood gas (PaO2/FiO2) in diagnosing ARDS. They found a sensitivity of 83% and specificity of 62% for moderate to severe ARDS. They demonstrated $SpO_2/FiO_2 \leq 315$ is sensitive for $PaO_2/FiO_2 \leq 300$ and $SpO_2/FiO_2 \leq 235$ is specific for $PaO_2/FiO_2 \leq 200$.[84] This study showed a reduced ultrasound accuracy compared to the previous studies mentioned with evidence of decreased sensitivity for consolidation.[84] One possible explanation for the decreased

diagnostic accuracy was their use of an algorithm other than the validated BLUE protocol.

Overall, the incorporation of lung ultrasound in place of CT is a validated, feasible approach for diagnosing ARDS with high diagnostic accuracy and correlation to EVLW. The development of the BLUE protocol will allow for doctors of patients in resource poor settings to utilize a validated, stepwise approach to the diagnosis of ARDS using lung ultrasound, leaving less room for interobserver variability.

Removal of PEEP

Although PEEP has an impact on the PaO_2/FiO_2 ratio, it is not feasible in low-resource settings and thus, the last modification in the Kigali criteria was its removal. In the Kigali study, the hospital had access to 6 ventilators that were all reserved for mechanically ventilated patients. Therefore, noninvasive ventilation, which also required the use of a mechanical ventilator, was not available.[8] The application of a minimum level of PEEP (5 cm H2O) can have a dramatic effect on the PaO_2/FiO_2 ratio, total shunt fraction, and V/Q mismatch that can improve the patient's PaO_2/FiO_2 ratio beyond the point where they meet criteria for ARDS.[41,2] Therefore, the elimination of PEEP may overestimate the number who would meet the criteria if PEEP were applied. However, the effect of PEEP is not universally predictable and the authors of the AECC criteria acknowledged its limited availability in resource poor settings.[27]

Estimate of ARDS Incidence Using the Modified Kigali and Berlin Criteria

The Kigali study by Riviello and colleagues was a six-week prospective observational study examining the primary outcome of hospital incidence of ARDS using the Kigali modification compared to the Berlin definition. In comparison to prior ARDS epidemiological studies, all adult patients admitted to the hospital were screened for hypoxemia (SpO_2< 90% or receiving supplemental oxygen) every day, which resulted in a 12% incidence (126/1046) of hypoxemia over the course of the study period. Using the Kigali modification, 4% (42/1046) screened positive for ARDS with a mortality rate of 50%, while 0% fulfilled the criteria for the Berlin definition due to lack of access to arterial samples and mechanical ventilation. The most common etiologies for ARDS were infections (44.1%, of which 10% were tuberculosis), trauma (29.4%) and surgery (25%). Only 21/42 patients were admitted to the ICU. Using two of the Kigali criteria and adding the requirement for a chest radiograph decreased the hospital incidence from 4% to only 1.6% because less than half of the patients with hypoxemia ever had a chest radiograph. The results of this study suggest a need for a validated, modified criteria for diagnosis of ARDS in resource-poor settings.[8]

Limitations

There are many limitations to this study. They include that it was a single center study with low generalizability for the rest of Africa given Rwanda's relatively low HIV rate.[8] Additionally, it had a less restrictive referral protocol, making the population incidence difficult to predict and possibly included those with cardiogenic pulmonary

edema, leading to a decreased accuracy in the estimated incidence of ARDS.[8] However, the most important limitation to this study was the unknown validity of the Kigali modification as a whole.[8]

Study Examining External Confirmation of Kigali Modification in the Netherlands

Vercesi and colleagues performed a single center observational study in the Netherlands to examine the external confirmation of the Kigali modification for moderate to severe ARDS in invasively mechanically ventilated patients. They performed four separate analyses: (1) Kigali vs. Berlin criteria; (2) Kigali vs. Berlin with lung CT as confirmation; (3) Kigali using PaO_2/FiO_2 instead of SpO_2/FiO_2 vs. Berlin; and (4) Kigali with a stricter LUS criteria vs. Berlin. They found the Kigali modification had a high sensitivity for ARDS but a moderate specificity. The specificity was increased when substituting PaO_2/FiO_2 for SpO_2/FiO_2 with a sensitivity of 0.96 and specificity of 0.86.[10] They found the best accuracy using stricter LUS criteria, improving the specificity to 0.93.[10] The overdiagnosis of ARDS was largely attributed to the use of LUS and using a stricter LUS criteria improved the ability of this criterion to differentiate ARDS.[10] One of the main limitations in this study was the inability to generalize to nonventilated patients, which is crucial for patients in resource-poor settings, like large hospitals having limited access to mechanical ventilators.[10] This study was also completed in a single center with a relatively small sample size that had moderate or severe ARDS [10] compared to the study in Kigali.[8]

Noninvasive Measurement to Rule Out Cardiogenic Pulmonary Edema

One of the recognized major limitations in the Riviello and colleagues Kigali modification is the possible inclusion of cardiogenic pulmonary edema. The authors ruled out cardiogenic pulmonary edema contributions either by a history of congestive heart failure, myocardial infarction (MI) in the chart, or bedside ECHO examining valvular pathology.[8] They failed to specify if any other objective measurements were used to rule out heart failure on ECHO besides the presence of valvular pathology.[8]

In the AECC criteria, PCWP was directly measured to rule out left heart pathology as a potential confounding factor but was later removed from the criteria due to the high degree of invasiveness in obtaining the measurements. Echocardiography has demonstrated promising results in evaluating elevated filling pressures by estimating mitral inflow signals and observing differences in pressures in the left atrium (LA) and left ventricle (LV) during diastole to predict elevated PCWP noninvasively.[85,86] Table 4 describes the ECHO Terminology used in the American Society of Echocardiography (ASE protocol).

Table 4. ECHO Terminology Used in the 2016 ASE Protocol

ECHO Terminology	Definition	Clinical Correlation
Mitral E wave velocity	Inflow signal from the LA to the LV in early diastole [87]	-The E wave reflects the pressure gradient between the LA and the LV. In early diastolic dysfunction, as the LV pressure increases, the pressure gradient shifts causing elevated LV pressure relative to LA pressure, and the E wave decreases. As diastolic dysfunction progresses, the LA pressure increases to overcome the LV pressure, and the E wave increases relative to the A wave[88]
Mitral A wave velocity	Inflow signal in late diastole including the time of atrial contraction [87]	-In early diastolic dysfunction, the heart relies on atrial contraction for LV filling, causing the A wave to increase. In later diastolic dysfunction, LA pressure increases to compensate for elevated LV pressure. This causes an increased inflow in early diastole (E wave) and relative decrease in the A wave[88,87]

ECHO Terminology	Definition	Clinical Correlation
Mitral E/A Ratio	Ratio of inflow signal in early diastole over late diastole [87]	-In early diastolic dysfunction, E/A ratio is decreased due to increased late diastolic filling reflecting atrial compensation. In late diastolic dysfunction, as the LA pressure increases and LV relaxation capacity decreases, the E/A ratio will continue increase.[88,87] -Increased values reflect increased diastolic dysfunction[87,89]
E'	-Measurement of LV relaxation in early diastole [87,89] -Inversely correlated with early diastolic pressure [87,89] -Can be measured from septal or lateral annulus [89]	-Doppler measurement that is a marker of LV relaxation and is inversely related to LA pressure -Decreased values reflect increased diastolic dysfunction[87,89]
Mitral E/e'	Mitral inflow velocity over diastolic relaxation[87,89]	-Increased ratio suggests increased mitral inflow relative to left ventricular relaxation [87,89] -Increased values reflect increased diastolic dysfunction[87,89]

ECHO Terminology	Definition	Clinical Correlation
LA Maximum volume index	Reflects chronic consequences of increased LV filling pressures[87,89]	Increased values reflect increased left sided filling pressures[87]

The ASE has presented guidelines used in estimating left ventricular filling pressures by echocardiography for both preserved and depressed ejection fraction (EF). EF is the fraction of blood ejected from the heart during systole, estimated by the volume of blood in the left ventricle immediately before and after systole, expressed as a percentage.[87] In patients with normal EF, they use E/e', Septal e' velocity, TR velocity and LA volume index to evaluate the diastolic dysfunction. [87,5] In patients with reduced EF, they used Mitral E/A ratio followed by E/e', TR velocity and LA volume index to estimate LV filling pressures.[87] The European Association of Cardiovascular Imaging (EACVI) and ASE released the first recommendations in 2009 and later modified them to a simpler version in 2016.[5] In 2017, Lancellotti and colleagues published the Euro-Filling study comparing the diagnostic accuracy of the 2009 and 2016 algorithms for predicting left ventricular filling pressure (LVFP) when compared to the invasive left heart catheterization.[5,90] They found an improvement in the diagnostic accuracy based on the 2016 recommendations and concluded that noninvasive estimation of LVFP can be mildly reliable and useful in a clinical setting.[90]

There are different types of filling patterns based on the grade of diastolic dysfunction. The spectrum extends from normal, to impaired relaxation, to "pseudonormal" filling, then to restrictive filling patterns.[87]

The ASE protocol is an algorithm that first separates patients based on EF.[87] In patients with a normal EF, if they have greater than two of the four criteria (Average E/e' > 14; Septal e' velocity < 7cm/s or Lateral e' velocity < 10cm/s; TR velocity> 2.8m/s; or LA volume index > 34ml/m^2), they are defined as having diastolic dysfunction with preserved EF.[87] If they have two of the four criteria, they are indeterminate, less than two they have normal diastolic function.[87]

In patients with reduced EF and patients with myocardial disease and normal EF, the algorithm starts with mitral inflow.[87] If the E/A ≤ 0.8 + E ≤ 50cm/s then the patient is noted to have a normal left atrial pressure (LAP).[87] If the E/A ≥ 2, then the patient is noted to have an increased LAP with Grade III Diastolic Dysfunction.[87] If the E/A ≤ 0.8 + E >50cm/s or E/A >0.8 < 2 then three follow up criteria are measured (average E/e' >14; TR velocity > 2.8 m/s, LA Volume index > 34ml/m^2).[87] If at least two of the three are negative, the patient is considered to have a normal LAP with Grade I Diastolic Dysfunction.[87] When at least two of the three criteria are positive, the patient is considered to have an increased LAP with Grade II Diastolic Dysfunction.[87]

Sugimoto and colleagues examined diastolic annular and mitral inflow velocities in estimating PCWP in patients with both systolic dysfunction, demonstrated by reduced EF, and diastolic dysfunction, demonstrated by preserved EF.[86] They evaluated 165 patients using echocardiographic examination to estimate PCWP >18mmHg confirmed

on right heart catheterization.[86] They demonstrated a high correlation of mean PCWP and E/A ratio.[86] When using E'≤ 8 and E/A ≥ 1.81 in the preserved ejection fraction (EF) group, they found a diagnostic accuracy of 94.0%, sensitivity of 87.5%, specificity of 94.7%, positive predictive value (PPV) of 63.6% and negative predictive value (NPV) of 98.6%.[86] When using E' ≤ 8 and E/A ≥ 1.16 in the reduced EF groups, they found a diagnostic accuracy of 89%, sensitivity of 84.9%, PPV of 77.8%, and NPV of 97.8%.[86] Overall, it was found that, after they account for EF, using E'<8 and E/A, had high diagnostic accuracy of predicting PCWP >18mmHg compared with E/E' derived estimations.[86]

Dokainish and colleagues examined noninvasive ECHO assessment of filling pressures compared with B-type natriuretic peptide (BNP), a hormone that has been found to correlate with ventricular stress and elevated left ventricular filling pressures, in estimating PCWP.[85] They found, when comparing the two noninvasive techniques, BNP and ECHO, ECHO measurements using E/Ea had a stronger association with PCWP >15mmHg.[85] They further subcategorized their patients based on EF with EF>50% and EF<50%.[85] They found with ECHO had a higher specificity for PCWP >15mmHg in patients with reduced EF compared to BNP.[85]

To summarize, noninvasive measurements of LVFP can be used in addition to the previously used measurements in the Kigali criteria, including evidence of valvular pathology on ECHO, history of heart failure and myocardial infarction (MI) with evidence of volume overload.

Timing of Onset of ARDS and Clinical Outcome

The timing of the presentation of ARDS can be crucial in the clinical outcome for the patient. One prospective multicenter study compared early (<48 hours) to late (>48 hours) onset of ARDS after admission to the hospital.[11] They found a higher in-hospital mortality rate and longer durations in ICU and mechanical ventilation in those who were diagnosed with late onset ARDS.[11] Another study examined 393 patients across 198 ICUs in 24 European countries, where 64.6% presented with early onset ARDS (within 48 hours ICU admission) and 35.5% had late onset ARDS (>48 hours after ICU admission). Although no difference in mortality was found between the two groups in this study, there was a statistically significant increase in ICU and hospital length of stay for late onset ARDS.[91] Another study performed a secondary class analysis on the two subphenotypes in ARDS from two randomized controlled trials (RCTs) and found class 2, the hyperinflammatory subphenotype, had progressive organ failure by day 3.[61] Although there have been studies comparing early and late onset ARDS using the Berlin criteria, there have not been any studies examining the time to diagnosis from arrival to the Emergency Department (ED) with the Berlin criteria compared to the noninvasive modified Kigali definition. Using noninvasive measures in the Kigali criteria to diagnose ARDS compared with the use of invasive tools in the Berlin criteria could lead to a more expeditious diagnosis of ARDS by allowing all the diagnostic tests to be performed at the bedside. This could decrease the time between onset and treatment, including noninvasive ventilation, protective lung ventilation, ECMO, and/or triage to an institution capable of these interventions.[3]

Many studies have examined the effect of timing in the use of ECMO in ARDS.[15] One single center retrospective study examined the early initiation of ECMO for patients with severe ARDS and found an improved mortality for early introduction of ECMO compared to conventional therapy with protective mechanical ventilation.[15] In this study, the average time to ECMO intervention after the diagnosis of severe ARDS was 1.9 +/- 1.4 days.[92]

A RCT in West China compared two ventilation strategies on patients diagnosed with ARDS who were on mechanical ventilation <48 hours total.[14] They compared the gold standard lung protective ventilation strategy with the airway pressure release ventilation (APRV) method.[14] The results showed that early administration of APRV led to a decreased length of mechanical ventilation, ICU stay, and an improvement in oxygenation and respiratory system compliance with decreased plateau pressure.[14]

Multiple studies have shown that early incorporation of noninvasive ventilation (NIV), such as CPAP, in patients with ARDS can allow them to avoid invasive mechanical ventilation (IMV).[21] The LUNG SAFE study examined the epidemiology of ARDS across 50 countries and found, of those treated with NIV on days 1 and 2 of ICU admission, 65% were able to avoid IMV.[93,21]

To summarize, the use of noninvasive technologies in the Kigali modification could enable early diagnosis of ARDS, allowing earlier allocation to the correct therapies, including NIV, protective ventilation, APRV, ECMO, and optimal approaches to fluid management, which are critical to delaying disease progression and/or reducing mortality in patients with ARDS. There is a lack of data comparing the time of onset of ARDS

using the Berlin criteria to the noninvasive Kigali modification beginning from the arrival to the emergency department, which would assist in outlining the optimal time to intervention or transport to a resource equipped institution.

METHODS

Study design

This will be a multi-center observational study comparing timing to diagnosis of ARDS using the Kigali modification and the Berlin criteria and calculating the diagnostic accuracy, including the sensitivity, specificity, positive predictive value and negative predictive value, of the Kigali modification using the Berlin definition as the gold standard.[92]

Study population and sampling

The study population will include patients presenting to the Boston Medical Center, Brigham and Women's Hospital, Massachusetts General Hospital, Beth Israel Deaconess Medical Center, Tufts Medical Center, Lahey Medical Center and St. Elizabeth Medical Center Emergency Departments with hypoxemia ($SpO_2 < 90\%$). The patients will be recruited over a 12-month period. Inclusion and exclusion criteria are detailed below (Table 5). Patients will be classified as mild, moderate, or severe ARDS based on the appropriate SpO_2/FiO_2 ratio in the Kigali modification and the PaO_2/FiO_2 ratio in the Berlin definition.

Table 5. Inclusion and Exclusion Criteria for Study Patients

Inclusion	Exclusion
1. All patients over the age of 18 and personally able or legal next of kin are able to provide informed consent 2. All patients will have hypoxemia <90% on presentation 3. SpO_2 <90% and/or receiving supplemental oxygen 4. All patients will have timing of onset of illness <7days prior to presentation	1. Any patients with elevated filling pressures based on ASE protocol using echocardiography or clinical evidence volume overload

A previous IRB submission to Boston Medical Center estimated the number of patients diagnosed with ARDS at Boston Medical Center annually to be 50. The estimated sample size in this study will be 350 based on the previous estimation of 50 from Boston Medical Center, multiplied by the seven facilities involved. Based on this sample size of 350, the minimum delectable effect size in mean time to diagnosis by a paired T test will be 0.150, which translates to a small effect size based on the Cohen's effect size measurements.[94] This was calculated using an alpha of 0.05, a beta of 0.2, and a standard deviation of 1.

Study variables and measures

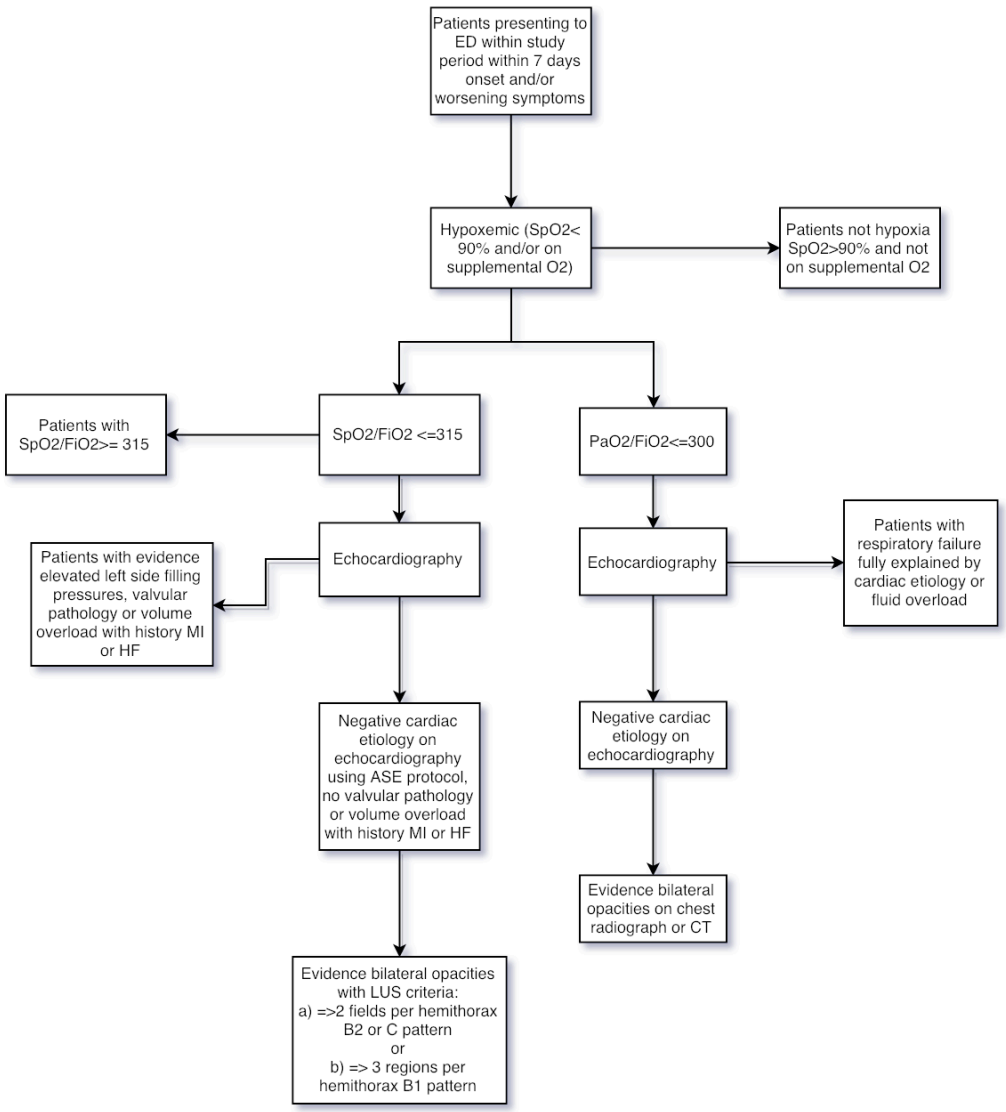
Demographic data collected will include age, gender, disease severity based on the Acute Physiology and Chronic Evaluation (APACHE) II score, comorbidities (i.e. neurological, cardiac, respiratory, gastrointestinal, renal, hematologic, infectious disease), patient category, i.e., medical or surgical, and potential cause for ARDS.[10]

The study's primary endpoint will be the time from the patient's presentation to the ED to the time to diagnosis of mild, moderate, and severe ARDS based on the

modified Kigali criteria compared to the Berlin definition. The secondary endpoint will be the diagnostic accuracy of the Kigali modification when using the Berlin criteria as the gold standard reference.

All patients presenting to the institutions' Emergency Departments with hypoxemia (SpO_2 < 90%) and/or on supplemental oxygen will be screened for ARDS using the Kigali modification and the Berlin criteria (Figure 1). If the patients meet the timing (< 7 days) and oxygenation criteria based on the Kigali modification (SpO_2/FiO_2< 315) and/or Berlin definition (PaO_2/FiO_2 ≤300), the patients will have a cardiac echo performed by an ECHO technician to rule out a cardiac etiology for the pulmonary edema. After ruling out a cardiac etiology, lung ultrasound profiles and chest radiographs or CT will be obtained. Lung ultrasound images will be obtained and interpreted by a pulmonary physician blind to the study. Two separate panels of intensivists will examine the data including the SpO2/FiO2, the PaO2/FiO2, chest radiograph or CT, and the interpretations of the lung ultrasounds and echocardiograms reported by the screening physicians. If the patients in the study do not meet the criteria of ARDS, they will be continued to be screened every 12 hours during their admission to evaluate for delayed onset of presentation. If the patients in the study meet the criteria of ARDS for one and not the other, they will be continued to be screened with the other criteria every 12 hours. For example, if they meet the Berlin criteria and not the Kigali criteria, they will continue to be screened with the Kigali criteria every 12 hours during their admission. If they meet the Kigali criteria and not the Berlin criteria, they would continue to be screened for the Berlin criteria every 12 hours during their admission.

Figure 1. Steps in the proposed study comparing the time to diagnosis of the Kigali Modification and the Berlin Definition.



The interpreting physicians will be randomized into two groups. Physicians in Groups 1 will evaluate the data based upon the modified Kigali criteria and physicians in Group 2 will analyze the data using the Berlin criteria.

Physicians will determine an ARDS diagnosis based on the Kigali modification if: (1) the patient presents <7 days from onset or worsening symptoms; (2) $SpO_2/FiO_2 < 315$; (3) negative cardiac etiology based on ASE protocol, and/or without valvular pathology, and/or 2 signs and symptoms of heart failure with a history of MI or heart failure; and (4) positive lung ultrasound (i.e., see Lung Ultrasound protocol).

Physicians will determine an ARDS diagnosis based on the Berlin definition if: (1) the patient presents < 7 days from onset or worsening symptoms; (2) $PaO_2/FiO_2 < 300$; (3) respiratory failure not fully explained by cardiac etiology with objective assessment e.g., ECHO; (4) positive bilateral opacities on either chest radiograph or CT; and (5) minimum PEEP 5 mmHg.

Lung Ultrasound protocol

The Lung Ultrasound protocol will be the stricter LUS protocol applied in the external confirmation Vercesi et al study, completed in the Netherlands (Table 6).[10] The LUS Protocol incorporates the lung profiles A, B and C taken from the BLUE protocol (Table 7).

Table 6. Strict Lung Ultrasound Protocol Used in the Vercesi Study Examining the External Confirmation of the Kigali Modification in the Netherlands

Lung Ultrasound Protocol
Positive Finding either:
a. At least 2 fields per hemithorax scored as B2 or C*[10]
b. At least 3 fields per hemithorax scored as B1 or greater*[10]
▪ If one lung zone has multiple patterns, it will be scored as the most severe pattern[10] ▪ Order severity: C>B2>B1>A[10]

Table 7. BLUE Profiles Used in the Strict Lung Ultrasound Protocol Developed by Vercesi and Colleagues When They Examined the External Confirmation of the Kigali Modification in the Netherlands

Blue Profiles		
Lung Profile	**View on Ultrasound**	**Correlated Syndromes**
A	▪ Predominant A lines with lung sliding at anterior surface in supine or half recumbent patients [4]	▪ Chronic Obstructive Pulmonary Disease (COPD) ▪ Embolism ▪ Status Asthmaticus ▪ Pneumonia [4]
B	▪ Anterior predominant B lines also referred to as Anterior Interstitial Syndrome with Lung Sliding	▪ Cardiogenic Pulmonary Edema ▪ Pneumonia [4]

	▪ B lines suggest juxtaposition of matter with different densities and echogenicity such as fluid and air [4] ▪ 3 or more B lines in single view are called B+ lines[4]	
A/B	▪ Anterior predominant A lines in one hemithorax and anterior predominant B lines on other hemithorax [4]	▪ Pneumonia[4]
C	▪ Anterior Consolidation [4]	▪ Pneumonia[4]

Lung Ultrasound Steps

Two clinicians trained in lung ultrasound blinded to the study will perform and interpret the lung ultrasound bedside. If two clinicians disagree, the results will be counted as interobserver variability and excluded from the analysis. Left and right chest walls will be subdivided into 6 regions on each side equaling 12 total regions based on the BLUE protocol.[4,10] The lines used to make the 12 lung zones will be the parasternal, paravertebral, anterior axillary, posterior axillary lines and a transverse line separating them into top and bottom segments.[10] The 12 lung regions will be scanned using a 5-MHz microconvex probe, scored by the screening physicians, and will be classified as patterns based on various lung ultrasound profiles defined in the BLUE protocol (Table 7) and will be separated into A, B and C patterns based on the Vercesi strict lung ultrasound protocol (Table 6).[10,4] The "A pattern" is defined as mainly A lines with lung sliding and less than 3 B lines.[104] A lines are horizontal lines that arise from the pleural line that

coincide with well aerated lung tissue.[10,4] The "B pattern" refers to 3 or more B lines with lung sliding.[10,4] B lines are vertical lines that appear like a "comet tail" and extend from the pleural line to end of the screen.[4,10] The B pattern is subdivided into B1 and B2, with the B1 pattern defined as 3 or more spaced out B lines with lung sliding.[10,4] The B2 pattern is defined as 3 or more B lines.[10] A "C pattern" has a tissue-like appearance with low echogenicity consistent with a consolidation.[10,4] Pleural effusions will be defined as detection of pleural fluid in 3 out of 6 regions in the hemithorax.[10] Because the neighboring lung can have atelectasis secondary to the effusion, these regions will be excluded.[10]

American Society Echocardiography Protocol

To exclude cases of pulmonary edema fully explained by cardiac etiology, the ASE protocol to estimate elevated left sided filling pressures in both preserved and reduced EF will be used in addition to presence of valvular pathology on ECHO and history of MI or heart failure in the chart with 2 or more signs and symptoms of volume overload (i.e. dyspnea, jugular venous distension, pitting edema). These symptoms of volume overload have a high specificity for congestion.[95,96] Table 8 outlines the criteria that qualify for a positive cardiac etiology, thereby ruling out ARDS.

Table 8. Criteria to Evaluate for Cardiac Etiology in the Kigali Modification in the Proposed Study

Positive Cardiac Etiology if at least one of the following:

▪ Presence of diastolic dysfunction based on ASE algorithm using tissue doppler and 2D ECHO
▪ Presence of valvular pathology on ECHO
▪ History of heart failure or MI in chart and 2 of the following:
  ▪ Dyspnea
  ▪ Jugular venous distension
  ▪ Pitting edema

Recruitment

Patients presenting to the Emergency Department in Boston Medical Center, Brigham and Women's Hospital, Massachusetts General Hospital, Beth Israel Deaconess Medical Center, Tufts Medical Center, Lahey Medical Center and St. Elizabeth Medical Center Emergency Departments with $SpO_2 < 90\%$ and/or on supplemental oxygen will be approached by the Research Assistant and asked for consent to participate in the study. If patients are not able to provide consent, the legal next of kin will be asked.

Data collection

The necessary data will be taken from the Electronic Medical Record and paper charts and recorded into a data spreadsheet in Excel. The data that is not included in the standard of care will be separately entered into the data spreadsheet in Excel by the

research assistant at the given facility. The data will be collected in a secure manner with protected health information (PHI) kept confidential and not used in the study. The data will be stored on a HIPAA compliant computer with confidentiality maintained throughout the entire study.

Data analysis

Categorical variables, including demographics, comorbidities, patient category (medical vs. surgical), and likely etiology of ARDS will be expressed as counts and percentages.

The primary outcome of the time to diagnosis of ARDS by the Berlin and Kigali criteria will be compared using a paired t test.

Diagnostic accuracy of the Kigali modification will be analyzed using the Berlin definition as a gold standard reference. Sensitivity, specificity, positive predictive value and negative predictive values will be calculated as percentages with 95% Confidence Intervals.

Timeline and resources

The study will take place from Fall 2019 to March 2021 (Table 9).

Table 9: Proposed Study Timeline

Fall 2019	IRB Submission and Application and Approval
January 2020-January 2021	Patient Recruitment
February 2021- March 2021	Data Analysis

Resources

Resources involved will be the funding required for the additional tests and interpretations involved in diagnosing ARDS with the Kigali criteria. It will also include the salaries of the investigators in the seven emergency departments in the Boston area, the research assistants doing hospital recruitment and the salary of one statistician performing the data analysis. Additionally, it will involve compensating the screeners involved in interpreting the lung ultrasound and echocardiography and the physicians making the diagnosis of ARDS.

Institutional Review Board

The recruitment and study protocols will be submitted for review to the Institutional Review Board (IRB) at the Boston University Medical Campus through the expedited common rule group 4, the section on collection of data through noninvasive procedures, and to the additional IRBs of the additional facilities.

CONCLUSION

Discussion

The results of this study will help determine the diagnostic accuracy of the Kigali modification using the Berlin criteria as the gold standard and whether the Kigali modification diagnoses ARDS earlier than the Berlin criteria. The timing to the diagnosis of patients presenting to the ED using the Berlin criteria alone and the Berlin criteria compared to the Kigali modification is not well studied. Measuring the timing to diagnosis will shed light on the clinical course that leads to the development of ARDS and potentially allow for earlier access to proper therapeutic intervention. Although there have been studies evaluating the timing of ARDS and prognostic outcome on arrival to ICU or on admission, there is a lack of research in examining time to presentation to the ED, which can be applied to lower income populations as hospital bed capacity is limited.

The outline of this study does have limitations. Because there are two groups of physicians evaluating one criteria, either the Kigali or Berlin, this could introduce bias into the study. However, given both the Kigali criteria and Berlin criteria are relatively objective and the imaging, including the echocardiography and the lung ultrasound, will be interpreted by separate physicians, the bias will be limited. Another limitation involves the location of the study. Given these medical centers are in the Northeastern region of the United States, most patients will be from the local area. Therefore, the study lacks generalizability to lower income settings like Rwanda. In addition, the 2016 ASE protocol, examining left sided filling pressures, was less reliable when compared to the direct measurement of the left heart catheterization in the EACVI Euro-filling study,

which demonstrated a sensitivity of 43% and a specificity of 75%.[90] The decreased sensitivity may be improved by providing the patient's clinical context, including the signs and symptoms of volume overload and valvular pathology, as was done in the original Kigali study. The exclusion of PEEP will likely overestimate the prevalence of ARDS by including patients who would not meet the ARDS criteria if a minimum PEEP of 5cmH_2O were applied. However, excluding PEEP will allow for the study population to be representative of low-income populations. Lastly, although lung ultrasound has demonstrated high accuracy compared to chest radiograph in diagnosing ARDS, in the Vercesi et al study, lung ultrasound overestimated ARDS when compared to CT. Based on the Vercesi study, a stricter LUS criteria will be used to increase its specificity.[10]

Summary

In summary, based on the literature review, ARDS is a disease with high mortality, inaccurate measures of global epidemiology and limited treatment options that have been shown to have benefits on mortality. With the global estimation of ARDS difficult to predict in low resource settings, a validated, modified definition using available tools in low-income populations will elucidate the epidemiology and etiologies of ARDS in these regions. With differing etiologies from high-income countries, low-income populations may respond to new treatments differently in clinical trials, leading to a revolution in management of ARDS according to its etiology. This novel approach to diagnosing ARDS will allow physicians to rapidly screen patients upon presentation to the ED in both high- and low-income countries, thereby evaluating the optimal timeline for therapeutic interventions in both populations.

Using noninvasive tools may lead to an earlier diagnosis of ARDS, allowing patients in need sufficient time to relocate to resource-equipped hospitals. The proposed study will attempt to address the gaps in the diagnosis and time to therapeutic intervention seen in low-income populations using noninvasive tools.

Clinical and/or public health significance

The benefits to diagnosing ARDS earlier in the course of the disease include the efficacious triage to ECMO, timely institution of protective ventilation management and choosing the optimal approach to fluid management based on the subphenotype.[44,62,15] Current research is underway exploring the use of mesenchymal stem cell therapy that may demonstrate improved outcomes if introduced earlier in the disease.[69,70] Additionally, patients who suffer from ARDS in low-income populations will be correctly diagnosed, potentially triaged to a higher level of care, and perhaps incorporated into clinical trials.

LIST OF JOURNAL ABBREVIATIONS

Am J Pathol	The American Journal of Pathology
Am J Respir Crit Care Med	American Journal of Respiratory and Critical Care Medicine
Anesthes	Anesthesiology
BMC Res Notes	BMC Research Notes
BMJ	BMJ: British Medical Journal
Br J Radiol	The British Journal of Radiology
Crit Care	Critical Care
Crit Care Resusc	Critical Care & Resuscitation Journal
Crit Care Med	Critical Care Medicine
Eur Heart J	European Heart Journal
Eur Respir	European Respiratory Journal
JAMA	The Journal of the American Medical Association
J Formos Med Assoc	Journal of the Formosan Medical Association
J Trauma Acute Care Surg	Journal of Trauma and Acute Care Surgery
J Clin Invest	Journal of Clinical Investigation
J Echocardiogr	Journal of the American Society of Echocardiography
NEJM	New England Journal of Medicine

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