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Acute Respiratory Distress Syndrome in Veterinary Medicine—The ARDSVet Definitions

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ABSTRACT

Objective: To use a systematic, evidence-based consensus process to develop updated definitions for acute respiratory distress syndrome (ARDS) in veterinary medicine to facilitate its recognition and diagnosis.

Design: International consensus conference series involving 12 multidisciplinary international content experts from three countries, using consensus conference methodology and implementation science. A systematic review of the literature was carried out for ARDS and acute lung injury in veterinary medicine. Updated definitions of ARDS were generated based on synthesis of human and veterinary literature. Consensus on the definitions was achieved through Delphi-style surveys involving the above subject matter experts. Draft recommendations were made available through industry specialty listservs for feedback, which was incorporated in the final definitions.

Results: Updated definitions were developed for Veterinary Acute Respiratory Distress Syndrome (ARDSVet) in small animals (dogs and cats) and large animals (equids). For small animals, 690 publications were identified for dogs and 99 were identified for cats in the initial literature search. Seventeen cats and 103 dogs with ARDS were represented across these publications. For the initial literature search in large animals, there were 83 equid, five camelid, 158 pig, 714 sheep and goat, and 270 cattle publications identified. Additionally, 1084 publications were found across all large animals that addressed interstitial lung disease. Five adult equids and 136 foals with ARDS were represented across these publications. The updated ARDSVet definitions incorporate criteria

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CT, computed tomography; HFNO, high-flow nasal oxygen; OI, oxygenation index; OSI, oxygen saturation index; PEEP, positive end-expiratory pressure; POCUS, point-of-care ultrasound; SIRS, systemic inflammatory response syndrome; SpO_2, oxygen saturation as measured by pulse oximetry; VetALI, veterinary acute lung injury (prior veterinary definition); ARDSVet, veterinary acute respiratory distress syndrome (prior veterinary definition).

Part of the material contained in this consensus statement was presented at the Annual Scientific Symposium of the Veterinary Comparative Respiratory Society in Providence, RI in October 2023. Draft definitions were presented at the International Veterinary Emergency and Critical Care Symposium in St. Louis, MO in September 2024.

for risk factors, origin and timing of pulmonary edema, and impaired oxygenation, with severity stratified by oxygenation and definitions for both intubated and nonintubated animals.

Conclusions: The evidence review and consensus process resulted in updated definitions that can be used to improve the recognition of veterinary ARDS as well as facilitate and standardize future research, including the development of an ARDS registry and eventual treatment recommendations.

1 | Introduction

Acute respiratory distress syndrome (ARDS) is a devastating clinical condition documented in both people and veterinary patients that is characterized by a peracute onset of respiratory distress. The definition of ARDS in human medicine has evolved significantly over the past three decades. The American-European Consensus Conference (AECC) led to the first broad consensus of definitions in 1994, where ARDS was defined as an acute onset of hypoxemia with a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ≤200 mm Hg, with bilateral infiltrates on thoracic radiographs in the absence of left atrial hypertension [1]. The term acute lung injury (ALI) was used to define a condition with the same variables but less severe hypoxemia (PaO_2/FiO_2 ratio ≤300 mm Hg). In 2007, the first clinically based consensus definitions on the veterinary syndromes of acute lung injury (VetALI) and acute respiratory distress syndrome (VetARDS) were described [2]. Five diagnostic criteria were published, with four being required and a fifth highly recommended [2]. These definitions were modeled along the lines of the AECC human definitions, and currently, no updated veterinary definitions exist. Some features of ALI/ARDS in the neonatal foal were recognized as unique; therefore, equine neonatal ALI/ARDS (EqNALI/EqNARDS) was similarly defined, but with a graded gas exchange inefficiency table to allow for normal developmental changes in gas exchange.

The Berlin definition of ARDS in adults was proposed in 2013 [3]. Major changes represented with these definitions included the addition of a definitive time frame for onset of clinical signs, removal of the criterion for pulmonary artery wedge pressure, and addition of a minimum level of positive end-expiratory pressure (PEEP) as well as mutually exclusive thresholds of PaO_2/FiO_2 ratios to stratify patients based on the severity of ARDS (mild, moderate, and severe) [3]. The term "acute lung injury" was removed from these definitions. Increasing recognition of the limitations of the Berlin definition in resource-limited settings, particularly with respect to the requirement of arterial blood gas analyses and advanced respiratory support through mechanical ventilation, led to the development of the Kigali Modification of the Berlin definition [4]. In 2023, an updated global definition of ARDS was published, which incorporated the developments in ARDS diagnosis and treatment since the COVID-19 pandemic, with consideration for a modified definition for use in resource-limited settings, thus broadening the scope of the definition [5].

In the years following the publication of the original definitions for VetALI and VetARDS, significant advances in veterinary respiratory critical care medicine have been made, with increasing use of advanced respiratory support therapies, novel modes of mechanical ventilation, and high-flow nasal oxygen (HFNO) [6–9]. The increasingly widespread use of lung ultrasonography in imaging both small and large animal patients with respiratory distress also merits evaluating whether this tool can be used to support a diagnosis of ARDS in a clinical setting [10, 11]. Despite these diagnostic and therapeutic advances, outcomes in veterinary patients with ARDS have not improved substantially [12, 13]. This remains a challenging condition to diagnose clinically, particularly with the wide variability in diagnostic and therapeutic resources that may impede early recognition and treatment in veterinary medicine. This variability also leads to challenges in conducting comparative research. Prompt and accurate recognition and stabilization of these animals in a critical care setting would be aided by definitions that are sensitive and broad enough to readily capture veterinary patients with ARDS, even at the risk of potentially overdiagnosing the condition in some instances, which may contribute to potentially unnecessary diagnostic tests and increased cost of care. Conversely, from a clinical research perspective, having less stringent and excessively broad definitions that are not highly specific can pose challenges with selecting patients for enrolment in prospective studies and make it difficult to draw definitive conclusions from studies that may include large numbers of patients with unconfirmed diagnoses. This underscores the importance of striking the right balance between definitions that are easy to apply and broad enough for a varied clinical setting, yet stringent enough to set the stage for high-quality future ARDS research in veterinary patients. Indeed, similar considerations in human medicine, including the widespread adoption of HFNO, the growing use of lung ultrasonography, the expansion of use of pulse oximetry in place of arterial blood gases, and the need for applicability in resource-limited settings, have been addressed in the updated global definition [5].

The objective of this veterinary consensus statement is to generate evidence-based updated veterinary ARDS definitions. These definitions should allow for improved recognition and treatment of veterinary ARDS patients across a wide variety of clinical settings while also serving as a basis for further clinical research and the potential future development of a veterinary ARDS and mechanical ventilation database.

2 | Methods

The Veterinary ARDS Working Group was established to comprise 10 veterinarians representing four different areas of specialty certification (Diplomates of both the American and European Colleges of Veterinary Emergency and Critical Care, both small animal and large animal; Diplomates of the American College of Veterinary Internal Medicine, both small animal and large animal) and two intensive care physicians (one working with adult and one with pediatric patients) specializing in the management

of ARDS in people to allow for a collaborative and translational approach. The Working Group was chosen to reflect individuals with a demonstrated clinical and research interest, as well as publications in the field of ARDS. The members of the Working Group represent both academic and private practice settings and are distributed across the United States, Canada, and the United Kingdom.

The Working Group completed the following tasks over the period from August 2021 through April 2024:

I. Domain creation
II. Review of veterinary and key human ARDS literature
III. Generation of updated veterinary ARDS definitions

2.1 | Domain Creation

The following domains were developed by the Working Group, under which the available evidence was used to draft statements:

Domain 1: Defining populations at risk and identifying risk factors for ARDS

Domain 2: Identifying diagnostic criteria used in small and large animals

Domain 3: Evaluating the use of advanced respiratory support therapies to diagnose ARDS

2.2 | Literature Review

The databases Embase, Scopus, Cochrane, PubMed, and CAB Abstracts were searched. Keywords, MeSH (**Me**dical **S**ubject **H**eadings), and title/abstracts were searched as appropriate to the database. For small animals (dogs and cats), the following terms were used: acute lung injury, acute respiratory distress syndrome, ALI, ARDS, respiratory distress syndrome, ground glass lung, hyaline membrane diseases, pulmonary surfactant, mechanical ventilator, lung injury, pulmonary atelectasis, diffuse alveolar damage, ground glass opacity, and acute hypoxemic respiratory failure. Small animal manuscripts published in 2007 or later were included with the intent of capturing literature published after the original veterinary ALI and ARDS definitions [2]. The search was limited to clinical veterinary articles only, and animal model studies were excluded in small animals.

The following terms were used in the large animal literature search (sheep, goats, cattle, horses, camelids, and swine): acute lung injury, acute respiratory distress syndrome, ALI, ARDS, respiratory distress syndrome, ground glass lung, hyaline membrane diseases, pulmonary surfactant, mechanical ventilator, lung injury, interstitial lung disease, pulmonary atelectasis, diffuse alveolar damage, and ground glass opacity. The large animal search included the years 1965 to present, with supplemental citation chaining as needed. Experimental studies for equine diseases were included in the review. The bibliographies of the retrieved articles were also reviewed. Review articles, experimental studies, and articles published in languages other than English were excluded for all species unless an English language summary was available.

Although the initial review included several veterinary species (dogs, cats, sheep, goats, cattle, horses, camelids, and swine), due to the high degree of variability in definition criteria used in many large animal publications, the subsequent consensus focuses on dogs and cats as representative of small animal patients and on horses as representatives of large animal patients. Assessment of other veterinary species will require further review in the future.

Following a review of included manuscripts, Working Group members under each domain generated summaries to be used to facilitate the development of draft definitions.

2.3 | Generation of Updated Veterinary ARDS Definitions

This process was conducted through an initial virtual working session held over a web-based platform[a] in which nine panelists participated. The main objective of this session was to generate draft definitions of ARDS in animals. This project was conducted in compliance with the Conducting and Reporting of Delphi Studies standards [14].

Panelists first participated in breakout sessions based on their assigned domain to review previously generated domain summaries. Domain summaries were then socialized with the entire working group to ensure a similar knowledge base across group members. This was subsequently followed by an online modified Delphi process that combined anonymous voting in survey rounds with subsequent rounds of moderated online discussion to generate draft definitions. The Delphi process survey was conducted using a structured questionnaire distributed via a web-based survey platform[b] to each of the participants. The voting process was anonymous to avoid any reciprocal influence. Questions were structured to include a 5-point Likert scale, with the consensus threshold set at 80% or greater agreement (i.e., 80% of responses marked as either "strongly agree" or "agree" on the Likert scale). Survey responses were grouped and stratified into low (score 1–2), intermediate (score 3), and high (score 4–5) levels of agreement. In addition to voting on each statement, panelists were invited to comment anonymously on the survey questions and provide suggestions to modify statement content and improve the wording, following an iterative process. For any questions that did not meet the consensus threshold of 80% following the first round of voting, a moderated online discussion was conducted among members. For each subsequent survey round, only questions that did not previously achieve consensus were included after modifications based on the panel comments and moderated discussion.

This was followed by an in-person workshop for members of the working group, wherein participants presented a summary of basic or clinical research in each of the domains. This was followed by additional discussion and two more rounds of voting to achieve consensus on all outstanding questions to generate draft definitions. All results are reported with the number of working group members who participated in the final round of voting.

These draft definitions were subsequently presented to various stakeholders through the email listservs of the American College of Veterinary Emergency and Critical Care, the European College of Veterinary Emergency and Critical Care, the American College of Veterinary Internal Medicine, the Japanese Veterinary Emergency and Critical Care Society, and the Veterinary Comparative Respiratory Society. Definitions were further refined based on these comments and suggestions.

2.4 | Statistical Analysis

Simple descriptive statistics (response rates and level of agreement for each statement) were used to describe approval rates between rounds.

2.4.1 | Domain 1: Defining Populations at Risk and Identifying Risk Factors for ARDS

2.4.1.1 | Background and Human Literature. Common etiologic risk factors exist that may predispose a patient to developing ARDS. The AECC definition classified these into direct and indirect lung injury categories. This distinction was removed from the Berlin definition with the rationale that identification of a risk factor leading to ARDS in a given patient, regardless of its indirect or direct nature, is most relevant when guiding therapy for the underlying disease leading to ARDS [1]. Risk factors outlined in the Berlin definition included pneumonia, nonpulmonary sepsis, aspiration of gastric contents, major trauma, pulmonary contusions, pancreatitis, inhalational injury, severe burns, noncardiogenic shock, drug overdoses, multiple transfusions or transfusion-related ALI, pulmonary vasculitis, and drowning.[3]

2.4.1.2 | Veterinary Literature.

2.4.1.2.1 | Cats and Dogs. For cats, there are very few reported cases in the literature documenting naturally occurring ALI or ARDS (17 cats documented across six studies). There are no clear age or sex predilections identified within these cats. Domestic shorthair cats were most frequently identified as being affected, although this is difficult to generalize given the small number of cats in these studies. Systemic inflammatory response syndrome (SIRS) and sepsis were consistently identified as risk factors for the development of ARDS in these studies, with other risk factors documented including toxic/inhalation injury, neoplasia, oxygen toxicity, acute kidney injury, mechanical ventilation, and adverse drug reactions [12, 13, 15–18].

For dogs, there are a greater number of cases reported in the literature documenting naturally occurring ALI or ARDS (103 dogs across 18 studies). SIRS and pulmonary aspiration of gastric contents are noted as potential risk factors most consistently across the larger studies, followed by pancreatitis, sepsis, trauma, mechanical ventilation, surgical interventions, pneumonia, neoplasia (both pulmonary and extrapulmonary), acute kidney injury, and babesiosis [12, 13, 19–26]. Other risk factors documented in single-case reports or case series include smoke inhalation, salt-water inhalation/drowning, inhalation of aerosol toxicants, adverse drug reactions, administration of intravenous lipid emulsions, rattlesnake envenomation, and blood product transfusions [27–34]. The reports of ARDS following blood product transfusions have significant confounding factors and describe respiratory signs at variable time frames post-transfusion that are not consistent with current guidelines outlined by the Association of Veterinary Hematology and Transfusion Medicine's Transfusion Reaction Small Animal Consensus Statement [25, 32, 35, 36].

In both cats and dogs, multiple potential risk factors were present for many cases, which limited the ability to differentiate those responsible. For example, all cases of canine babesiosis had at least one additional risk factor, such as SIRS and blood transfusion administration. Diagnosis of ALI and ARDS was not homogenous across all studies, and as noted in people, clinical and histopathologic diagnosis (in cases where both were present) were not always concordant [37].

2.4.1.2.2 | Equids. Similar to the small animal literature, few case reports of ARDS exist in equids. The variable nomenclature and absence of a consistent definition prior to 2007 made identification of cases even more difficult. Based on the 2007 veterinary consensus definitions, three naturally occurring cases of ALI following near drowning and smoke inhalation were described in adult horses (>1 year of age), but no case reports met the criteria for ARDS [38–40]. All adult horses with ALI survived with treatment. ARDS/ALI was considered likely in one additional adult horse with smoke inhalation and one donkey with influenza, the latter of which died despite medical management [39, 41]. Experimentally, "likely ARDS/ALI" was induced by injection of perilla mint ketones (six adult horses) and induction of gram-negative bacteremia (11 ponies) [42, 43].

In contrast, more cases of ARDS/ALI have been described in juvenile equids with confirmed ARDS/ALI in 23 foals (<24 h to 8 months) and likely ARDS/ALI in 113 cases including 107 horse and six donkey foals (1 day to 11 months). There were a total of 136 cases [44–56], including 63 colts, 56 fillies, and 17 foals of unknown sex. A variety of breeds were represented, with Thoroughbreds being most common, followed by Standardbreds and Warmbloods, consistent with the predominant breeds in the study populations. The vast majority of - ARDS/ALI appeared to be associated with bacterial or viral pulmonary or systemic infection. *Rhodococcus equi* ($n = 30$) and equine influenza virus ($n = 21$) were the most common pathogens, followed by *Pneumocystis carinii* ($n = 15$), *Chlamydia psittaci* ($n = 15$), *Streptococcus zooepidemicus* ($n = 13$), *Klebsiella pneumoniae* ($n = 11$), equine viral arteritis virus ($n = 9$), and a variety of other bacteria. Equine herpes virus 1 ($n = 1$), 2 ($n = 10$), 4 ($n = 4$), and 5 ($n = 4$) were also identified. Treatment was attempted in 61 cases, and 23 (38%) foals survived. Of the 38 nonsurvivors, 20 died and 18 were euthanized. Overall, no sex or breed predilection was identified, but ARDS was more common in young equids, with only five patients being older than 11 months and one case being older than 2 years of age.

2.4.1.3 | Working Group Recommendations.

a. We propose removing the term "acute lung injury" from the updated veterinary definitions for the sake of clarity. (*Agreement: 9/9*)

TABLE 1 | Probable risk factors for veterinary acute respiratory distress syndrome (ARDS)

Risk factor	Level of agreement among working group members
Aspiration injury	9/9
Systemic inflammatory response syndrome	8/9 (1/9 neutral)
Sepsis	9/9
Acute pancreatitis	9/9
Aerosolized toxin inhalation	9/9
Drowning	7/7
Trauma: - Thoracic - Extrathoracic	8/9 (1/9 neutral)
Smoke inhalation	9/9
Rhodococcus equi infection in horses	8/9 (1/9 neutral)
Equine influenza infection in horses	8/9 (1/9 neutral)

TABLE 2 | Possible risk factors for veterinary acute respiratory distress syndrome (ARDS)

Risk factor	Level of agreement among working group members
Transfusion of blood products	7/7
Ventilator-induced lung injury	7/7
Pneumocystis carinii infection in horses	6/7 (1/7 neutral)
Other mixed bacterial infections in horses	7/9 (2/9 neutral)
Other viral infections in horses	8/9 (1/9 disagree)

b. We propose grouping risk factors into "*probable*" and "*possible*" based on the level of evidence present in both small and large animals. (*Agreement: 9/9*)

c. We define "probable" risk factors as those that are either supported by multiple reports of ARDS with strong temporal associations or documented in patients with ARDS that met prior consensus definitions, with the absence of other likely risk factors (see Table 1). (*Agreement: 9/9*)

d. We define "possible" risk factors as those that are only supported by sporadic case reports without a clearly confirmed diagnosis of ARDS or those that were documented in patients with multiple risk factors present, where causal association could not be definitively determined (see Table 2). (*Agreement: 9/9*)

e. There should be new or worsening respiratory distress within 1 week of a known or suspected clinical insult. (*Agreement: 9/9*)

Probable and possible risk factors identified by the Working Group are summarized in Tables 1 and 2.

2.4.2 | Domain 2: Identifying Diagnostic Criteria Used in Small Animals and Large Animals

2.4.2.1 | Background and Human Literature. Developing criteria to establish the key characteristics of hypoxemia and diffuse pulmonary infiltrates associated with critical injury or illness is crucial to the diagnosis of ARDS. Additionally, in human medicine, an acute diagnosis of ARDS is useful for assessing the global burden of the disease, which can help direct resources toward prevention and treatment measures. The COVID-19 pandemic rapidly altered the landscape of ARDS and has increased the urgency of expanding definitions and evaluating treatment options in people.

Each human consensus statement, starting with the AECC definitions through the most recent Global Definition, has sequentially tried to refine diagnostic criteria and use advanced diagnostic techniques to more specifically stratify the severity of disease and pulmonary distribution of lesions [1, 3, 5]. Initial efforts focused on intubated and mechanically ventilated patients in well-resourced intensive care units. However, with the increasing use of HFNO, current definitions have also included patients with acute hypoxemic respiratory failure receiving this modality [5, 57].

Finally, ARDS is also recognized in patients in settings where advanced monitoring and therapeutic interventions are not available, prompting the Kigali Modification of the Berlin definition and the incorporation of lower fidelity diagnostic criteria in the recent Global Definition for use in resource-limited settings [4, 5, 57]. ARDS may be defined in these settings without the need for arterial blood gas analysis, the use of mechanical ventilation and positive end-expiratory pressure, or HFNO. To stratify hypoxemia, pulse oximetry (SpO_2, oxygen saturation as measured by pulse oximetry) in lieu of arterial blood gas analysis allows for assessment of the SpO_2/FiO_2 ratio rather than the PaO_2/FiO_2 ratio when SpO_2 is ≤97%. While the SpO_2/FiO_2 ratio is less invasive and more widely available, limitations include inaccuracies in SpO_2 measurement and flattening of the oxyhemoglobin dissociation curve when SpO_2 is >97%, leading to an uninformative SpO_2/FiO_2 ratio [4, 5, 57].

In addition, the incorporation of lung and thoracic ultrasonography in place of traditional imaging modalities such as chest radiographs or computed tomography (CT) has been accepted in the Global Definition of ARDS [5]. While CT has the highest sensitivity for identifying pulmonary edema, its use is limited by availability and transport needs of the critical patient [58]. As such, point-of-care ultrasound (POCUS) is emerging as an alternative imaging modality with comparable performance to chest radiography in adult and pediatric humans, with particular appeal in resource-limited settings [5, 58]. Biomarkers, though explored in a research setting, have not been included in clinical definitions of ARDS at this time [59].

2.4.2.2 | Veterinary Literature. A review of the veterinary literature revealed that the diagnostic criteria used for ARDS were widely variable, with some publications using older human definitions or the Havemeyer definitions, while others relied

upon histopathological findings. One publication used the Berlin definition, and the remainder used a combination of history and clinical progression along with thoracic radiographs to suggest a presumed diagnosis of ARDS [6, 12, 13, 18, 20, 22, 31, 50, 51]. Of important note, histopathology is not required in human medicine for a diagnosis of ARDS.

In prior veterinary definitions, the severity of hypoxemia was defined based on the PaO_2/FiO_2 ratio [2]. However, when considering the widespread availability of pulse oximetry over arterial blood gas analysis in veterinary medicine, the inclusion of the SpO_2/FiO_2 ratio in lieu of the PaO_2/FiO_2 ratio in an updated definition is enticing, with the caveat of inaccuracy in pulse oximetry in many patients [60]. The early adoption of SpO_2/FiO_2 ratios in veterinary ARDS has been explored in two studies, and recently SpO_2/FiO_2 ratios have been evaluated to assess HFNO failure [12, 13, 61, 62]. Several veterinary studies have evaluated the SpO_2/FiO_2 ratio in small animals and indicate good to excellent correlation between SpO_2/FiO_2 and PaO_2/FiO_2 ratios in dogs under various conditions with, however, variable cutoffs of equivalency [63–65]. A study in mechanically ventilated dogs found that a PaO_2/FiO_2 ratio of 300 was equivalent to an SpO_2/FiO_2 ratio of 223, and a PaO_2/FiO_2 ratio of 200 was equivalent to an SpO_2/FiO_2 ratio of 188 [63]. Similarly, SpO_2/FiO_2 ratios of 153, 203, and 253 were found to correspond to PaO_2/FiO_2 ratios of 100, 200, and 300, respectively, in mechanically ventilated dogs [66]. A single experimental study in cats evaluating several models of pulse oximeters found widely variable correlation of SpO_2 values with PaO_2, depending on the model and probe placement site [67]. Limitations with the use of pulse oximetry include inaccuracies in SpO_2 measurements in small animals and uncertainty with the FiO_2 delivered to the patient when oxygen is administered by face mask or nasal oxygen delivery methods that do not provide flows that consistently meet the patients'- demand, thereby allowing entrainment of room air and dilution of the delivered FiO_2 (i.e., nasal prongs and nasal cannulas). In addition, when dogs pant or are tachypneic, inspiratory flow rates can further decrease the ability to evaluate FiO_2. For precise FiO_2 determination, mechanical ventilation or the use of HFNO exceeding 1 L/kg/min or 30 L/min (total) improves the accuracy of the SpO_2/FiO_2 ratio calculation. The SpO_2/FiO_2 ratio thresholds suggested by the Working Group are generated from the veterinary data as well as extrapolation from human thresholds.

The hallmark of ARDS on thoracic imaging is diffuse pulmonary infiltrates, consistent with capillary leak. Most veterinary reports of ARDS rely on documentation with thoracic radiographs, with CT and POCUS being a distant second and third [12, 13]. Cost and availability considerations result in thoracic radiography being the typical initial imaging modality of choice in most veterinary patients. CT is ideal, but it is expensive and not widely available. CT is better able to detect heterogenous lung injury and may additionally be used to judge recruitment following increasing levels of PEEP [68]. POCUS will likely play an increasing role in cage/stall-side imaging in the veterinary patient. The use of ultrasound has had limited assessment in canine patients with ARDS [11]. Evidence on the utility of lung ultrasound for diagnosing ARDS is even more limited in horses, as no studies have evaluated its use in horses with confirmed ARDS, despite its widespread clinical application in the diagnosis of other equine respiratory diseases, such as bacterial pneumonia [10, 69]. A recent report in seven foals with acute interstitial pneumonia suggested good conformity between thoracic ultrasound and postmortem pulmonary findings [52].

While POCUS is widely available in veterinary medicine, and the ability to detect B-lines representing parenchymal infiltrates with this modality is high, POCUS is not specific for ARDS, as noncardiogenic pulmonary edema of other etiologies and cardiogenic pulmonary edema may present with similar ultrasonographic findings. The lack of left atrial enlargement in conjunction with other ultrasound findings suggestive of noncardiogenic pulmonary edema, such as pleural line abnormalities, may permit ruling out congestive heart failure in veterinary patients, although these remain highly dependent on operator skill and training [70, 71].

A literature review of described, naturally occurring equine ARDS showed that a confirmation of the diagnosis is challenging due to heterogeneity in terminology and reported diagnostic findings within and across studies. Confirmation of hypoxemia, when reported, has relied on PaO_2 and/or PaO_2/FiO_2 ratios on room air and with no ventilatory support. The use of SpO_2 to detect hypoxemia in awake horses or foals is not reported. Detection of bilateral pulmonary infiltrates in cases with confirmed hypoxemia has been performed through thoracic radiography, with limited information on the use of thoracic ultrasound [51]. Specific diagnostics to rule out fluid overload or left-sided heart disease beyond clinical signs are not described for any study.

2.4.2.3 | Working Group Recommendations. Given abundant human evidence that the characteristic histopathological changes associated with ARDS (evidence of diffuse alveolar damage—hyaline membranes, interstitial edema, cell necrosis, and proliferation) are time dependent and evolve from an initial exudative phase (within the first 7–10 days) to a subsequent proliferative and fibrotic phase, it was clear that requiring or adding histopathological criteria to the definitions would limit the clinical usefulness of these definitions [72, 73]. The Working Group also sought to provide diagnostic criteria that could be employed seamlessly across a wide range of clinical settings and resource availability, in line with the new Global ARDS Definitions [5].

Specifically, regarding the requirement for thoracic imaging to diagnose ARDS, the Working Group members agreed that some form of thoracic imaging establishing alveolar infiltrates was essential. However, considerations included noninclusion of the term "bilateral" when discussing alveolar infiltrates, given that unilateral disease can progress to bilateral diffuse disease, which is also acknowledged in the human pediatric definitions [57]. Additionally, having a requirement for documentation of bilateral infiltrates would preclude the inclusion of large animal patients since logistical challenges related to patient size and radiographic techniques frequently result in the inability to obtain dorsoventral or ventrodorsal images. The inclusion of lung ultrasonography was considered important both from the standpoint of large animal resource availability and as a reflection of the increasing use of POCUS in small animal emergency and critical care medicine as a point-of-care imaging tool where thoracic radiographs or CT may be difficult to obtain in unstable patients in respiratory distress [10, 11, 58].

With respect to the exclusion of cardiogenic pulmonary edema and fluid overload as causes when evaluating patients with alveolar infiltrates and acute hypoxemic respiratory failure, the Working Group agreed that requiring echocardiography or a measurement of pulmonary capillary wedge pressure to diagnose ARDS would amount to a significant diagnostic barrier, since these tools are not widely available across most veterinary care settings in both small and large animals. However, it was also not deemed appropriate to use either just history or physical examination, or just thoracic radiographs in isolation to rule out cardiogenic pulmonary edema or fluid overload.

Thus, the Working Group recommends that:

a. ARDS is a clinical diagnosis. Histopathology is not required to confirm a clinical diagnosis of ARDS. (*Agreement: 9/9*)

b. *Evidence of hypoxemia*: Confirmation of hypoxemia is required for the diagnosis of ARDS. A low PaO_2/FiO_2 ratio (in the absence of hypercapnia if on room air) OR an SpO_2/FiO_2 ratio can be used to confirm this. Arterial blood gas analysis is preferable, where possible. Specific SpO_2/FiO_2 ratio thresholds are outlined in Table 3. (*Agreement: 7/7*)

c. *Thoracic imaging*: Thoracic imaging demonstrating diffuse pulmonary infiltrates using CT, radiography, or thoracic ultrasound is required. Ongoing studies are needed to demonstrate whether any modality is preferable for a given species and clinical setting. (*Agreement: 9/9*)

d. *Exclusion of cardiogenic pulmonary edema*: Left-sided congestive heart failure and fluid overload as the cause of pulmonary infiltrates should be ruled out when diagnosing ARDS. Ultrasound (echocardiography, POCUS) is useful; however, thoracic radiography as well as history and physical examination findings may be used to support ruling out left-sided congestive heart failure and fluid overload as the cause of the patient's respiratory failure. (*Agreement: 9/9*)

e. *Presence of inflammatory airway fluid:* The presence of neutrophilic inflammation and high protein levels in airway fluid collected through tracheal wash or bronchoalveolar lavage are an optional supporting criterion when diagnosing ARDS caused by extra-pulmonary etiologies. (*Agreement: 6/7*)

2.4.3 | Domain 3: Evaluating the Use of Advanced Respiratory Support Therapies to Diagnose ARDS

2.4.3.1 | Background and Human Literature. Seven key adult and pediatric human publications were used to guide the updated small animal ARDS definitions. Beginning with the Berlin definition of ARDS and moving to the more recent Global D-efinitions, the inclusion of oxygenation thresholds and the requirement for advanced respiratory support in the form of mechanical ventilation have been key features [3, 5, 57].

2.4.3.2 | Veterinary Literature. Fifty-one publications that included dogs and 17 publications that included cats were reviewed for this domain, but there were insufficient data to separate dogs and cats. Two studies evaluated the use of HFNO in dogs with hypoxemic respiratory failure but did not specifically focus on patients with ARDS [7, 8]. Ten publications discussed the use of mechanical ventilation in dogs and cats with ARDS [6, 12, 13, 18, 21, 28, 29, 31, 74, 75]. When considering the use of advanced respiratory therapies for small animal ARDS patients, mechanical ventilation was primarily employed in dogs and cats with presumed ARDS; most other patients not placed on mechanical ventilation were euthanized. Overall, small numbers of patients in these reports precluded making an evidence-based definition of ARDS using ventilatory or HFNO parameters alone. Ultimately, the human literature, particularly the pediatric ARDS definitions and publications describing access to care in resource-limited settings, was found most useful to the recommendations made in this domain [3–5, 57].

2.4.3.3 | Working Group Recommendations. A requirement for advanced support, such as invasive mechanical ventilation (IMV) or HFNO, was not added to these definitions given that this could preclude inclusion of large numbers of animals that may otherwise satisfy clinical criteria but do not receive advanced support. This could be due to logistical, financial, or other reasons, or euthanasia early in the course of disease, prior to the initiation of such support, particularly in large animals. However, it was deemed prudent to add objective thresholds for those patients that do receive such support as outlined below. These thresholds are also outlined in Table 3.

a. We propose stratifying veterinary patients into three groups:
   - IMV-ARDS
   - Nonintubated ARDS
   - Patients at risk for ARDS *(Agreement: 10/11)*

b. ***IMV-ARDS***: We propose stratifying veterinary IMV-ARDS patients into two levels of severity defined as below:
   - *Mild/moderate ARDS*: PEEP of 5 cm H_2O or higher AND *should fulfill one of the below*:
     - PaO_2/FiO_2 ratio >100 and ≤300
     - SpO_2/FiO_2 ratio >150 and ≤315 (with SpO_2 ≤97%)
   - *Severe ARDS*: PEEP of 5 cm H_2O or higher AND *should fulfill one of the below*:
     - PaO_2/FiO_2 ratio ≤100
     - SpO_2/ FiO_2 ratio ≤150 (with SpO_2 ≤97%)

AND

The patient fulfills all other required diagnostic criteria for ARDS. Patients may move from one category to another throughout their disease course.

(*Agreement: 11/11*)

c. ***Nonintubated ARDS***: We propose that nonintubated veterinary ARDS patients should be stratified as below:
   - *Equines >24-h old*: PaO_2 ≤60 mm Hg
   - *Equines <24-h old*: PaO_2 ≤45 mm Hg
   - For animals receiving supplemental oxygen: HFNO: flow rate >1 L/kg/min or total >30 L/min (small animals only) OR supplemental oxygen with known FiO_2
     WITH
   - *Mild/moderate ARDS*: *should fulfill one of the below*
     - PaO_2/FiO_2 ratio >100 and ≤300
     - SpO_2/FiO_2 ratio >150 and ≤315 (with SpO_2 ≤97%)
   - *Severe ARDS: should fulfill one of the below*

TABLE 3 | The updated ARDSVet Definitions

Criteria that apply to all ARDSVet categories			
Risk factors	Precipitated by a known or suspected acute predisposing risk factor or clinical insult		
Origin of edema	Left-sided congestive heart failure (L-CHF) and fluid overload as the cause of pulmonary infiltrates should be ruled out when diagnosing ARDS. Ultrasound (echocardiography, POCUS) is useful; however, thoracic radiography, history, and physical examination findings may be used to support ruling out L-CHF and fluid overload		
Timing	New or worsening respiratory distress within 1 week of known or suspected clinical insult		
Thoracic imaging	Thoracic imaging demonstrating diffuse pulmonary infiltrates using CT, radiography, or thoracic ultrasound[a] is required.		
Airway fluid**	****Optional Supporting Criterion***: Neutrophilic inflammation and high protein levels in airway fluid collected through tracheal wash or bronchoalveolar lavage.		
Criteria that apply to specific ARDSVet categories			
		IMV-ARDS[d]	**Non-intubated ARDS**
Oxygenation[c,d,e]	**Severity** ↓	*Intubated, mechanically ventilated patients with PEEP of 5 cm H_2O or higher **AND** must fulfill one of the criteria below*	*Equines >24h old: $PaO_2 \leq 60$ mm Hg*
			Equines <24h old: $PaO_2 \leq 45$ mm Hg
			For all animals receiving supplemental oxygen:
			HFNO: flow rate >1 L/kg/min or total >30 L/min OR supplemental oxygen with known FiO_2 ***WITH:***
	Mild/Moderate	PaO_2:FiO_2 ratio > 100 and ≤ 300 ***OR***	
		SpO_2/FiO_2 ratio[b] > 150 and ≤ 315 (with $SpO_2 \leq 97\%$)	
	Severe	PaO_2:FiO_2 ratio ≤ 100 ***OR***	
		SpO_2/FiO_2 ratio[b] ≤ 150 (with $SpO_2 \leq 97\%$)	

Abbreviations: ARDS = acute respiratory distress syndrome; CT = computed tomography; HFNO = high-flow nasal oxygen; IMV = invasive mechanical ventilation; L-CHF = left-sided congestive heart failure; PEEP = positive end-expiratory pressure; POCUS = point of care ultrasound; SpO_2 = oxygen saturation as measured by pulse oximetry

[a]Thoracic radiographs or CT are preferred; however, ultrasound can be considered if radiographs or CT are not available. The ultrasound operator should be well trained in the use of ultrasound for identifying loss of lung aeration (e.g., multiple B lines and/or consolidations) and other ultrasound findings suggestive of noncardiogenic pulmonary edema (e.g., pleural line abnormalities).

[b]Modified oxygenation criteria can be applied in settings in which arterial blood gas and/or HFNO, and mechanical ventilation are not routinely available.

[c]For pulse oximetry, ensure an adequate waveform and oximeter placement. SpO_2/FiO_2 ratio is not valid above saturation values of 97%. Pulse oximetry is not recommended for diagnosis if a hemoglobin abnormality is suspected (e.g., methemoglobinemia or carboxyhemoglobinemia).

[d]For all severity categories of IMV ARDS, a minimum PEEP of 5 cm H_2O is required. Patients may move from one category to another throughout their disease course.

[e]If altitude is >1,000m, apply the following correction factor: (PaO_2 or SpO_2)/FiO_2 x (barometric pressure/760)

- PaO_2/FiO_2 ratio ≤100
- SpO_2/FiO_2 ratio ≤150 (with SpO_2 ≤97%)

AND

The patient fulfills all other required diagnostic criteria for ARDS. Patients may move from one category to another throughout their disease course.

(*Agreement: 10/11*)

d. ***Patients at risk for ARDS***: We propose that patients at risk for ARDS be defined as below:
   - *Equines >24-h old*: PaO_2 ≤60 mm Hg
   - *Equines <24-h old*: PaO_2 ≤45 mm Hg
   - Small animals: PaO_2/FiO_2 ≤300 mm Hg OR SpO_2 <88%

AND

The patient does not fulfill all the other required diagnostic criteria for ARDS.

(*Agreement: 10/11 [one member disagreed]*)

3 | Discussion

The updated veterinary ARDS definitions seek to build upon the previously published veterinary ALI and ARDS definitions and more recent human adult and pediatric ARDS definitions [2, 5, 57]. In describing probable and possible risk factors for ARDS, the Working Group also acknowledges that myriad causes of ARDS, including emerging viral causes of pneumonia as well as many drugs and toxins, are reported in people and should be considered possible, even if not conclusively proven yet in veterinary species.

These updated definitions aim to incorporate evolutions in diagnostic testing (such as POCUS) and therapies available for veterinary patients with ARDS (such as HFNO) while remaining accessible and relevant for veterinary care settings with limited resources that may not be able to access arterial blood gas analysis or advanced therapies such as mechanical ventilation. Specifically, the definitions account for the emergence of noninvasive support for veterinary patients with acute hypoxemic respiratory failure in the form of HFNO therapy. This modality represents an alternative to conventional oxygen therapy that delivers heated and humidified medical gas at adjustable flow rates, up to 60 L/min, and FiO_2 up to 100%, via nasal cannulas. HFNO therapy can provide reliable FiO_2 in addition to humidification, resulting in improved patient tolerance. It can also result in improved lung mechanics through reduction of anatomical dead space and provision of low-level PEEP [76]. HFNO therapy is a promising option in small animal patients and foals with acute hypoxemic respiratory failure that require escalating oxygen support [9, 77]. Potential avoidance of the need for intubation and escalation to mechanical ventilation is perhaps its most attractive attribute in veterinary emergency and critical care medicine, given that mechanical ventilation can be cost prohibitive and labor intensive. The inability to provide mechanical ventilation often results in an outcome of euthanasia for dogs and cats with ARDS [76]. Additionally, providing a category of "nonintubated ARDS" that accounts for patients receiving HFNO will help capture those subsets of patients for whom mechanical ventilation may not be an option and who may otherwise have been euthanized.

These definitions also include a category of patients at risk for ARDS. This category was proposed to define patients that are hypoxemic but may not yet fulfill all the other required diagnostic criteria for ARDS, including imaging findings. The Working Group agreed that defining a group of patients at risk for ARDS was useful to determine and study the epidemiology of disease progression in veterinary patients and identify potential avenues for disease prevention. Of note, this category should be used with caution and not used to make definitive prognostic or treatment recommendations to pet owners.

These definitions also include the option to utilize pulse oximetry in lieu of arterial blood gas analysis to confirm hypoxemia when the latter is unavailable, with the caveat that the SpO_2 should be ≤97% (due to the shape of the oxyhemoglobin dissociation curve). While a few veterinary studies have described the correlation between the SpO_2/FiO_2 ratio and the PaO_2/FiO_2 ratio in acutely hypoxemic awake dogs and mechanically ventilated dogs, to the authors' knowledge, this has not been analyzed in clinical studies in cats [63, 65, 67]. Canine studies reveal that the SpO_2/FiO_2 ratio is likely to have a stronger correlation with the PaO_2/FiO_2 ratio in anesthetized, mechanically ventilated dogs than in awake dogs breathing room air, with one study documenting that in ventilated dogs with an SpO_2 of 80%–97%, the SpO_2/FiO_2 ratio had a strong correlation with the PaO_2/FiO_2 ratio [63]. In this population of mechanically ventilated dogs, the linear regression equation developed predicted that SpO_2/FiO_2 ratios of 188 and 223 would correspond to PaO_2/FiO_2 ratios of 200 and 300, respectively. To the authors' knowledge, no veterinary studies have investigated the correlation between SpO_2/FiO_2 ratio and PaO_2/FiO_2 ratio in ARDS patients receiving HFNO therapy. We chose to use the SpO_2/FiO_2 ratio cutoffs of 150 and 315, respectively, in these definitions to align with the current human ARDS definitions [5]. While we acknowledge that the incorporation of the SpO_2/FiO_2 ratio may incorrectly categorize some patients as having ARDS, the potential benefit of providing a noninvasive alternative to arterial blood gas analysis that could identify certain subsets of patients with ARDS earlier outweighs this risk. It is clear, however, that additional studies are needed, particularly in cats, to better understand the utility and limitations of the SpO_2/FiO_2 ratio.

The inclusion of lung ultrasound in these definitions is another significant change, which aligns with a similar evolution in adult and pediatric human ARDS diagnosis [5, 57]. POCUS is widely available, relatively inexpensive, and increasingly employed in veterinary emergency and critical care settings. The Working Group endorsed the use of lung ultrasound by trained operators to detect diffuse pulmonary infiltrates, especially when patients are too unstable for thoracic radiography and CT may not be feasible. When performed by trained operators, lung ultrasound in humans can detect changes such as pleural line abnormalities that may help distinguish the noncardiogenic pulmonary edema seen with ARDS from B-lines and consolidations associated with other forms of pulmonary edema [78, 79]. Additional studies are necessary in veterinary patients across a range of clinical settings and operator skill sets and training levels to further evaluate lung ultrasound in ARDS patients.

The updated definitions are intended to cast a wide net to help promptly identify more veterinary patients with ARDS in the absence of a single gold standard diagnostic test, while maintaining enough stringency to standardize and facilitate future research. Additionally, similar to adult and pediatric human definitions, these veterinary definitions allow for noninvasive alternatives to diagnostic criteria, such as arterial blood gas analysis, that may be more easily employed in limited resource settings. Animals in these settings may exhibit clinical features consistent with ARDS despite not meeting strict diagnostic criteria, highlighting the importance of their inclusion for both research and clinical considerations. Future research comparing patient populations included within these categories will shed important light and further our understanding of the clinical construct of ARDS.

For patients with ARDS that are receiving mechanical ventilation (IMV-ARDS), these definitions do not currently include measures such as the oxygenation index (OI) and oxygen saturation index (OSI). The Working Group considered the inclusion of these two measures to stratify the severity of hypoxemia in these current definitions, similar to the current pediatric ARDS consensus [57]. OI is a measure that can reflect more globally the severity of lung injury when compared to the PaO_2/FiO_2 ratio, since the former accounts for the impact of mechanical ventilation settings, changes in lung compliance, and pulmonary shunts [80]. OSI is a similar measure to the OI that utilizes pulse oximetry in lieu of arterial blood gas analysis. Both OI and OSI have been found to be predictive of outcome in humans with ARDS [80, 81]. Two studies evaluating mechanically ventilated dogs, including those with ARDS, have reported the OI and OSI, with one study reporting that the OSI was strongly correlated with the OI throughout the duration of mechanical ventilation; however, neither study reported on the prognostic value of these indices

[12, 74]. Despite the strong evidence in humans regarding the utility of these indices to assess disease severity as well as aid in prognostication in patients with ARDS, the overall paucity of evidence in veterinary patients led to the exclusion of these indices from the current definitions. However, future prospective studies exploring these indices in both dogs and cats with ARDS would be extremely valuable. The Working Group chose to, instead, stratify this group of IMV-ARDS patients based on the PaO_2/FiO_2 and SpO_2/FiO_2 ratios, similar to the nonintubated ARDS category. It is important to note that a nonintubated ARDS patient receiving HFNO cannot be compared equally to an IMV-ARDS patient that is receiving PEEP and that this consideration will be important for future research studies utilizing these definitions. The Working Group acknowledges that this is an inherent limitation of not incorporating the degree of IMV support into the stratification categories for this patient population; however, given the need to balance spectrum of care considerations as well as the lack of physiologic evidence to recognize the precise degree of support provided by HFNO in veterinary patients, this was considered an acceptable compromise. This is an area that will likely require refinement in future iterations of the veterinary ARDS definitions.

3.1 | Knowledge Gaps to Guide Future Research Suggested by the Working Group

1. Evaluation of the sensitivity and specificity of point-of-care lung ultrasound diagnosis of veterinary ARDS in different species among operators with varied training in diverse clinical settings using different acquisition/interpretation protocols.
2. Evaluation of the role of subphenotypes of ARDS and both diagnostic and prognostic biomarkers that may aid in clinical decision-making.
3. Therapeutic interventions in veterinary ARDS:
   - Evaluation of HFNO machine settings and outcomes in ARDS
   - Mechanical ventilation in veterinary ARDS: evaluation of OI and OSI, driving pressures as a therapeutic target, and evaluation of outcome differences between different modes of mechanical ventilation
   - Pharmacotherapies in veterinary ARDS: glucocorticoids, bronchodilators, furosemide, and other therapeutic agents
4. Evaluation of epidemiology and long-term outcomes in patients diagnosed with ARDS across diverse resource settings utilizing the updated veterinary ARDS definitions through the creation of a veterinary ARDS registry.

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Conflicts of Interest

The authors declare no conflicts of interest.

Endnotes

[a] Zoom Video Communications, Qumu Corporation, San Jose, CA.

[b] Google Forms, Google Inc., Mountain View, CA.

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