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Prognosis Factors of the Co-Presentation of ARDS and Sepsis: A Systematic Review

Stephanie M. Brown [a*], Hla Myo Thwe [b], Roshan Goswami [c], Tania M. Cobena Bravo [c], Ademilua Oluwatobi Iyanuoluwa [d], Frederick Ferguson [e], Maryfortune Ugoeze Chilaka [f], Shaheen Sultana [g], Shazia Noreen Durrani [h], Ayodele Paul Ogunro [c], Kayode Aguda [i], Regina Azipu [j], Onyinye Ezewudo [k], Ngozika Grace Obiefuna [k], Shwetha Gopal [l] and Jovita Echere [m]

[a] Queens University College of Medicine (QUCOM), Barbados.
[b] University of Medicine 1 Yangon, Myanmar.
[c] American University of Antigua College of Medicine, Antigua, Barbuda.
[d] All Saints University School of Medicine, Dominica.
[e] Department of Family Medicine, Summa Health, USA.
[f] Chukwuemeka Odumegwu Ojukwu University College of Medical Sciences, Nigeria.
[g] Siddhartha Medical College (SMC), India.
[h] Faisalabad Medical University (FMU), Pakistan.
[i] Obafemi Awolowo University College of Health Sciences, Nigeria.
[j] University of Calabar College of Medical Sciences, Nigeria.
[k] College of Medicine, University of Nigeria Nsukka, Nigeria.
[l] Bassett Medical Center, USA.
[m] The University of Texas, Health Science Center at Houston School of Public Health, USA.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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**Corresponding author: E-mail: smbrownmed@gmail.com;*

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Systematic Review Article

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ABSTRACT

Background: The co-occurrence of acute respiratory distress syndrome (ARDS) and sepsis presents a critical challenge in critical care medicine. ARDS involves diffuse alveolar damage, leading to severe hypoxemia, while sepsis entails a dysregulated host response to infection, resulting in systemic inflammation and organ dysfunction. This study aims to provide a comprehensive understanding of the contributing factors to ARDS and sepsis co-presentation, highlighting its significance in clinical scenarios, often leading to severe respiratory compromise and increased mortality risk. The findings offer original insights into potential biomarkers and therapeutic strategies that could inform future research and clinical practices.

Methods: This systematic review adheres to PRISMA 2020 guidelines. Inclusion criteria cover studies on ARDS and sepsis co-presentation (2014–2024), diverse designs, human participants, and English articles. Electronic searches (PubMed, Embase, Cochrane Library) utilized MeSH terms and free-text. Manual searches ensured comprehensive exploration. Two reviewers screened titles/abstracts and conducted full-text eligibility assessments. Data extraction involved a narrative synthesis, focusing on study outcomes, strengths, and limitations. Results were organized into tables for clarity.

Results: Of 1624 studies, 343 duplicates were removed. 1281 studies underwent title/abstract screening, with 149 assessed for eligibility. 138 studies were excluded, yielding 11 included studies. These studies, involving 4086 patients, utilized diverse methodologies. Mortality risk, molecular phenotypes, immune responses, potential biomarkers, and fluid management strategies were identified. Limitations included study heterogeneity and biases.

Conclusion: This systematic review provides nuanced insights into ARDS and sepsis co-presentation. The originality of this review lies in its identification of novel biomarkers and therapeutic avenues, which may contribute to refining clinical approaches and informing future research. Despite valuable findings, limitations exist in study methodologies and challenges in establishing causality. The review underscores the need for ongoing updates and emphasizes the importance of prospective, multicenter studies with standardized methodologies for robust evidence and improved clinical practices.

Keywords: ARDS; acute respiratory distress syndrome; sepsis; co-presentation; systematic review; mortality; molecular phenotypes; immune responses; biomarkers; fluid management.

1. INTRODUCTION

The co-occurrence of acute respiratory distress syndrome (ARDS) and sepsis represents a critical intersection in the landscape of critical care medicine [1–3]. ARDS is characterized by diffuse alveolar damage leading to impaired gas exchange and severe hypoxemia, while sepsis involves a dysregulated host response to infection, often resulting in systemic inflammation and organ dysfunction [4–7]. Understanding the intricate relationship between these conditions is paramount for improving clinical outcomes.

The pathogenesis of ARDS in the context of sepsis involves a complex interplay of immune responses, inflammatory mediators, and endothelial dysfunction [8,9]. Sepsis-induced inflammation can trigger and exacerbate the pulmonary manifestations of ARDS, creating a challenging clinical scenario characterized by severe respiratory compromise and increased mortality risk [10,11]. Unraveling the specific factors contributing to the development of ARDS in the setting of sepsis is crucial for advancing our understanding of the disease mechanisms and, consequently, refining therapeutic approaches.

This systematic review aims to comprehensively analyze existing literature, ranging from observational studies to molecular investigations, to identify and elucidate the factors that contribute to the co-presentation of ARDS and sepsis. By exploring the molecular pathways, immunological responses, and potential

biomarkers associated with this complex interplay, the review seeks to provide a nuanced understanding of the pathophysiological mechanisms underpinning the simultaneous occurrence of ARDS and sepsis. This knowledge may pave the way for targeted interventions, improved risk stratification, and enhanced management strategies for patients navigating the intricate interplay of these critical conditions.

2. METHODS

This systematic review is reported in accordance with PRISMA Statement 2020 guidelines [12].

2.1 Eligibility Criteria

Inclusion Criteria

1. Studies investigating the co-presentation of acute respiratory distress syndrome (ARDS) and sepsis.
2. Articles published between 2014 and 2024.
3. All study designs, including observational studies, prospective and retrospective cohort studies, and genetic causal inference methods.
4. Studies conducted on human participants.
5. Articles available in English.
6. Studies providing information on factors contributing to the co-occurrence of ARDS and sepsis.

Exclusion Criteria

1. Studies published before 2014 or after 2024.
2. Animal studies.
3. Studies not written in English.
4. Studies with insufficient information on the co-presentation of ARDS and sepsis.
5. Reviews, case reports, editorials, and conference abstracts.
6. Studies focusing solely on either ARDS or sepsis without addressing their co-presentation.

2.2 Information Sources

A comprehensive search was conducted across electronic databases, including PubMed, Embase, and the Cochrane Library, to gather relevant studies for the systematic review. The search string for PubMed is as follows: ((("respiratory distress syndrome"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "respiratory distress syndrome"[All Fields] OR "ards"[All Fields]) AND ("sepsis"[MeSH Terms] OR "sepsis"[All Fields])) AND ((observationalstudy [Filter]) AND (humans [Filter]) AND (2014:2024[pdat])).

Manual search methods were employed to scrutinize journals and conferences, ensuring an exhaustive exploration of the literature. The search, encompassing articles without linguistic or chronological constraints, focused exclusively on human-based studies.

2.3 Search Strategy

The search strategy centered on key terms related to the co-presentation of acute respiratory distress syndrome and sepsis. MeSH terms such as "respiratory distress syndrome" and free-text terminologies like "ARDS," "sepsis," and "observational study" were utilized. The search was meticulous, covering PubMed and extending until January 10, 2024, to ensure a thorough identification of relevant studies.

2.4 Study Selection

Two independent reviewers initially evaluated titles and abstracts of the identified studies, followed by a comprehensive assessment of the full content against predetermined eligibility criteria. Inclusion criteria focused on studies investigating the co-occurrence of ARDS and sepsis in human participants, employing diverse methodologies. Studies not meeting these criteria were systematically excluded.

2.5 Data Extraction and Synthesis

A narrative synthesis approach was adopted for data extraction. Information from selected studies was systematically analyzed to discern nuances and the overall effectiveness of different factors contributing to the co-presentation of ARDS and sepsis. Each study's outcomes, along with a rigorous analysis of strengths and limitations, were documented. The extracted data were meticulously organized into tables, including details such as author, year, title, study design, sample size, population characteristics, key findings, and notes/comments. The synthesis emphasized crucial insights and recommendations for clinical practices, as well as potential directions for future research.

2.6 Justification and Stakeholder Impact

The co-occurrence of acute respiratory distress syndrome (ARDS) and sepsis represents a

significant challenge in critical care medicine, with high morbidity and mortality rates. Despite extensive research on ARDS and sepsis individually, the simultaneous presentation of these conditions remains underexplored. This study is crucial as it aims to fill this gap by systematically reviewing the factors contributing to ARDS and sepsis co-presentation, which is essential for improving clinical outcomes and patient management. The findings of this review are expected to benefit several key stakeholders:

1. **Clinicians:** By identifying molecular phenotypes and potential biomarkers, this study provides clinicians with tools to enhance early diagnosis, risk stratification, and targeted interventions, ultimately leading to better patient outcomes.
2. **Researchers:** The study offers a foundation for future research on ARDS and sepsis co-presentation, encouraging further exploration into the pathophysiological mechanisms and therapeutic strategies specific to this intersection.
3. **Healthcare Policymakers:** Insights from this study can inform guidelines and policies that promote the adoption of precision medicine approaches in the management of ARDS and sepsis, leading to more effective allocation of resources.
4. **Patients and Families:** By advancing the understanding of ARDS and sepsis co-presentation, this study aims to contribute to improved treatment strategies, thereby enhancing the quality of care and survival rates for patients facing these critical conditions.

3. RESULTS

Of 1624 studies identified from database searching, 343 duplicates were removed. 1281 studies were screened for titles and abstracts of which 149 were sought for full-text eligibility. Of these 138 did not meet the eligibility criteria. The PRISMA flowchart is presented in Fig. 1.

This systematic review incorporated 11 studies investigating sepsis-associated acute respiratory distress syndrome (ARDS) across various methodologies. A total of 4086 patients were included in this study. The characteristics of the included studies are listed in Table 1.

In a prospective multicenter observational study, Okazaki and colleagues [13] focused on patients expected to receive mechanical ventilation for more than 48 hours. Mortality was found to be higher in the ARDS subgroup within the non-sepsis group. Notably, the effect of ARDS on 6-month outcomes depended on the presence or absence of sepsis. However, the findings are dependent on available follow-up information, limiting generalizability to all patient populations.

Sinha et al. [14] conducted a latent class analysis (LCA) and retrospective application of ARDS phenotype classification models on the VALID (N=1140) and EARLI (N=818) cohorts. Two molecular phenotypes were identified: hypoinflammatory and hyperinflammatory. Findings showed strong concordance between sepsis and ARDS phenotypes. The hyperinflammatory phenotype was associated with adverse clinical markers. Limitations include potential bias from retrospective application and variations in treatment responses across populations.

In a prospective observational study Yan and colleagues [15] involved 62 patients with sepsis-associated ARDS, decreased CD8+ T cell counts and proliferation were observed in non-surviving ARDS patients. Increased expression of the inhibitory receptors PD-1 and Tim-3 was associated with worse organ function and longer shock duration. Low CD8+ T cell percentages and increased inhibitory molecule expression were linked to worse survival. However, the observational design limits establishing causal relationships, and potential confounding factors were not fully addressed.

Hernández-Beeftink and colleagues [16] conducted an observational study involving 687 peripheral whole-blood samples from septic patients (264 with ARDS) and revealed a significant association between whole-blood mitochondrial DNA (wb-mtDNA) copies and 28-day survival in ARDS patients. However, this association was not observed in non-ARDS patients. While supporting the potential of wb-mtDNA copies as an early prognostic biomarker, the observational design precludes establishing causal relationships.

Villar et al. [17] led a biomarker panel study using ELISA and retrospective analysis, which included 232 adult septic patients, of which 72 had ARDS. A panel including RAGE, CXCL16, Ang-2, and PaO2/FiO2 effectively predicted ARDS, with biomarkers improving prediction for ICU death. Limitations include a retrospective approach,

potential selection bias, and the focus on specific biomarkers, possibly overlooking the full complexity of sepsis and ARDS.

In a prospective single-center observational study, Gaudet and colleagues [18] involved 72 severe sepsis patients; low endocan levels at ICU admission were associated with ARDS development at 72 hours. Endocan values above 5.36 ng/mL had a protective effect against ARDS development. However, the study's single-center nature may limit generalizability, and the relatively small sample size warrants cautious interpretation.

Reilly et al. [19] employed genetic causal inference methods in 703 septic subjects, with a focus on European ancestry (n=404), plasma ANG2 was strongly associated with ARDS risk. The study highlighted a specific genetic variant (rs2442608C) linked to higher ARDS risk. Genetically predicted plasma ANG2 was also associated with ARDS risk, with plasma ANG2 mediating a significant portion of the rs2442608C-related ARDS risk. Limitations include potential unmeasured factors influencing associations and limitations in capturing the full diversity of septic patients.

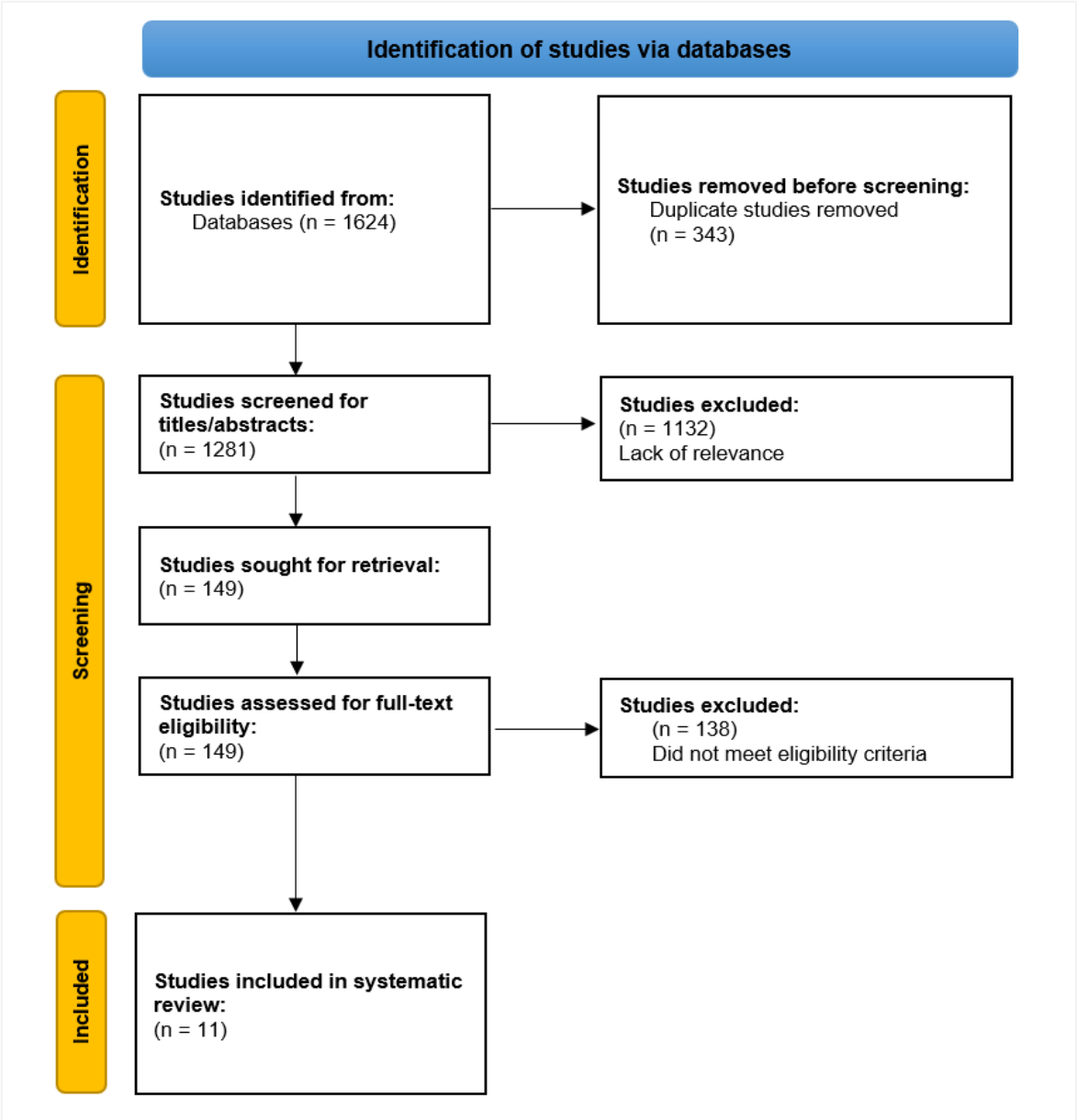

Fig. 1. PRISMA flowchart depicting the study selection process

Table 1. Characteristics of the included studies

Author-Year	Study Design and Methods	Participants	Key Findings	Limitations
Okazaki-2023 [13]	Analysis of a prospective multicenter observational study	Patients expected to receive mechanical ventilation for more than 48 hours	-Mortality higher in ARDS subgroup in non-sepsis group -Effect of ARDS on 6-month outcomes depended on the presence or absence of sepsis	Dependent on available follow-up information; findings may not generalize to all patient populations
Sinha-2023 [14]	Latent class analysis (LCA), retrospective application of ARDS phenotype classification models	VALID cohort (N=1140), EARLI cohort (N=818); Two molecular phenotypes identified - hypoinflammatory (VALID: 70.5%, EARLI: 64.8%) and hyperinflammatory (VALID: 29.5%, EARLI: 35.2%)	-Strong concordance between sepsis phenotypes and previously identified ARDS phenotypes -Hyperinflammatory phenotype associated with higher plasma pro-inflammatory cytokines, more vasopressor use, more bacteremia, lower protein C, and higher mortality -In PROWESS-SHOCK, response to activated protein C differed by phenotype (p=0.0043) -In VASST, no treatment interaction with the type of vasopressor observed (p=0.72)	Findings are based on the VALID and EARLI cohorts; generalizability to other sepsis cohorts may be limited; applying ARDS phenotype models retrospectively may introduce bias; treatment responses may vary in different populations and settings
Yan-2022 [15]	Prospective observational study	62 patients with sepsis-associated ARDS	-Decreased CD8+ T cell counts and proliferation in non-surviving ARDS patients -Increased PD-1 expression associated with worse organ function, and Tim-3 with longer shock duration -Low CD8+ T cell percentages and increased inhibitory	Observational design; causal relationships not established; potential confounding factors not fully addressed

Author-Year	Study Design and Methods	Participants	Key Findings	Limitations
			molecule expression associated with worse survival	
Hernández-Beeftink-2021 [16]	Observational study	687 peripheral whole-blood samples from septic patients (264 with ARDS)	-wb-mtDNA copies significantly associated with 28-day survival in ARDS patients -wb-mtDNA copies not associated with survival in non-ARDS patients	Observational study design; causal relationships not established
Villar-2021 [17]	Biomarker panel study using ELISA; Retrospective analysis	232 adult septic patients (152 required invasive mechanical ventilation, 72 had ARDS)	-Panel including RAGE, CXCL16, Ang-2, and PaO2/FiO2 predicted ARDS (AUC = 0.88) -Biomarkers improved prediction by clinical markers for ICU death	Retrospective analysis; potential for selection bias; limited to specific biomarkers and may not capture the full complexity of sepsis and ARDS
Gaudet-2018 [18]	Prospective single-center observational study	72 patients with severe sepsis	-Low endocan levels at ICU admission associated with ARDS development at 72 hours -Endocan values > 5.36 ng/mL had a protective effect against ARDS development	Single-center study may limit generalizability; the study size is relatively small
Reilly-2018 [19]	Genetic causal inference methods - Mendelian randomization, quantitative trait loci (QTL) analysis, linear regression, logistic regression, mediation analysis	703 septic subjects (European ancestry: n=404); Plasma ANG2 measured in ICU admission; Rs2442608C variant associated with higher ARDS risk	-Plasma ANG2 strongly associated with ARDS (OR 1.59 per log, 95% CI 1.35-1.88) -Rs2442608C variant associated with higher ARDS risk (adjusted OR 1.38, 95% CI 1.01-1.87) -Genetically predicted plasma ANG2 associated with ARDS risk (adjusted OR 2.25, 95% CI 1.06-4.78) -Plasma ANG2 mediated 34%	Focused on European ancestry subjects; unmeasured factors may influence the associations observed; the sample size may have limitations in capturing the full diversity of septic patients

Author-Year	Study Design and Methods	Participants	Key Findings	Limitations
			of rs2442608C-related ARDS risk	
Fuller-2015 [20]	Retrospective observational cohort study	Mechanically ventilated patients with severe sepsis and septic shock (n=122)	-No association between sepsis-associated cardiac dysfunction and ARDS incidence or mortality -Higher BMI associated with progression to ARDS	-Retrospective design with inherent limitations -Impact of cardiac dysfunction on ARDS should be further studied
Mansur-2015 [21]	Prospective observational study	404 patients with sepsis-associated ARDS	-Statin therapy improved 28-day survival in severe ARDS patients -Statin therapy associated with more vasopressor-free days and less ECMO therapy	Potential confounders not fully addressed; need for further study to elucidate the potential effect of statin therapy
Caltabeloti-2014 [22]	Prospective observational study	32 patients with septic shock and ARDS	-Early fluid loading improved hemodynamics and oxygenation but worsened lung aeration -Lung ultrasound detected changes in lung aeration	Small sample size; the study focused on short-term effects; long-term outcomes not assessed
Chang-2014 [23]	Retrospective cohort study	296 adult patients admitted with severe sepsis and septic shock	-No significant association between IV fluid volume and ARDS development -Serum albumin and APACHE II score informative for ARDS development	Retrospective design with inherent limitations; potential unmeasured confounders influencing ARDS development

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; BMI: Body Mass Index; CI: Confidence Interval; ECMO: Extracorporeal Membrane Oxygenation; ELISA: Enzyme-Linked Immunosorbent Assay; ICU: Intensive Care Unit; LCA: Latent Class Analysis; mtDNA: Mitochondrial DNA; OR: Odds Ratio; PD-1: Programmed Cell Death 1; QTL: Quantitative Trait Loci; RAGE: Receptor for Advanced Glycation End-products; TIM-3: T Cell Immunoglobulin Mucin-3; VASST: Vasopressin and Septic Shock Trial; VALID: Vasopressin in Septic Shock and Sepsis; wb-mtDNA: Whole-Blood Mitochondrial DNA

Fuller and colleagues [20] conducted a retrospective observational cohort study of 122 mechanically ventilated patients with severe sepsis and septic shock, sepsis-associated cardiac dysfunction, which showed no association with ARDS incidence or mortality. Instead, higher BMI was associated with progression to ARDS. The retrospective design has inherent limitations, and the impact of cardiac dysfunction on ARDS warrants further investigation.

Mansur et al.'s [21] prospective observational study involving 404 patients with sepsis-associated ARDS found that statin therapy improved 28-day survival in severe ARDS patients. Statin therapy was associated with more vasopressor-free days and less extracorporeal membrane oxygenation (ECMO) therapy. Limitations include potential confounders not fully addressed, emphasizing the need for further study to elucidate the potential effect of statin therapy.

Caltabeloti and colleagues' [22] prospective observational study of 32 patients with septic shock and ARDS, early fluid loading improved hemodynamics and oxygenation but worsened lung aeration. Lung ultrasound effectively detected changes in lung aeration. Limitations include a small sample size and the study's focus on short-term effects, with long-term outcomes not assessed.

Chang et al. [23] conducted a retrospective cohort study of 296 adult patients admitted with severe sepsis and septic shock; they found no significant association between intravenous (IV) fluid volume and ARDS development. Serum albumin and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were informative for ARDS development. The retrospective design introduces inherent limitations, and potential unmeasured confounders might influence ARDS development.

4. DISCUSSION

This systematic review examined 11 studies investigating the co-presentation of ARDS and sepsis, encompassing diverse methodologies and a total of 4086 patients. The findings offer a comprehensive understanding of the intricate relationship between these critical conditions. Okazaki et al. [13] identified a heightened mortality risk in the ARDS subgroup within the non-sepsis group, emphasizing the complex interplay between ARDS, sepsis, and patient outcomes. Sinha et al. [14] revealed distinct molecular phenotypes, linking them to clinical outcomes and treatment responses. Yan et al. [15] uncovered immune responses associated with survival in sepsis-associated ARDS, shedding light on potential therapeutic targets. Hernández-Beeftink et al. [16] identified whole-blood mitochondrial DNA as a potential prognostic biomarker, presenting a promising avenue for early risk assessment. Villar et al. [17] proposed a biomarker panel predicting ARDS, enhancing risk stratification for ICU death. Gaudet et al. [18] highlighted endocan as a potential predictor of ARDS development, contributing to prognostic insights. Reilly et al. [19] explored genetic determinants, unveiling a specific variant associated with higher ARDS risk, enriching our understanding of genetic influences. Fuller et al. [20] shifted focus to cardiac dysfunction in severe sepsis, while Mansur et al. [21] suggested a potential role for statin therapy in improving outcomes. Caltabeloti et al. [22] and Chang et al. [23] delved into fluid management strategies, offering valuable insights into hemodynamic optimization.

This systematic review aligns with and extends existing literature on ARDS and sepsis, providing a nuanced synthesis of recent evidence. Notably, our findings corroborate the well-established link between ARDS and sepsis, emphasizing the need for targeted interventions in this high-risk population [24]. Sinha et al.'s identification of molecular phenotypes echoes recent advancements in precision medicine, acknowledging the heterogeneity within septic populations [25–27]. Additionally, the immune dysregulation identified by Yan et al. aligns with the evolving understanding of sepsis as an immune-mediated disorder [28,29]. Hernández-Beeftink et al.'s exploration of mitochondrial DNA parallels the growing interest in biomarkers for early sepsis recognition and prognostication [30,31]. Villar et al.'s biomarker panel resonates with efforts to enhance risk prediction, reflecting the broader trend toward precision medicine in critical care [32]. Reilly et al.'s genetic analysis adds depth to the exploration of genetic influences on sepsis outcomes [33].

Despite the valuable insights provided, this systematic review has inherent limitations. The inclusion of studies may not capture recent advancements, necessitating ongoing updates. Heterogeneity in study designs and patient populations may introduce variability, impacting

the generalizability of findings. Additionally, the reliance on observational studies poses challenges in establishing causal relationships. Future research should focus on prospective, multicenter studies with standardized methodologies to enhance generalizability and minimize biases.

5. CONCLUSION

In conclusion, while this systematic review offers valuable insights into the co-presentation of acute respiratory distress syndrome (ARDS) and sepsis, a critical examination of the evidence reveals certain limitations. The reliance on observational studies with diverse methodologies introduces inherent biases and challenges in establishing causal relationships. Heterogeneity among the studies complicates evidence synthesis and raises concerns about the generalizability of findings. The retrospective application of ARDS phenotype models and variations in treatment responses across populations underscore the need for cautious interpretation. Additionally, the dynamic nature of critical care medicine necessitates ongoing updates to capture any advancements. Despite these limitations, the review provides a nuanced understanding of factors contributing to ARDS in sepsis, emphasizing the importance of prospective, multicenter studies with standardized methodologies for robust evidence and improved clinical practices.

6. IMPLICATIONS

This systematic review offers significant implications for clinical practice and research in critical care medicine. The identification of distinct molecular phenotypes and potential biomarkers, such as whole-blood mitochondrial DNA, provides valuable insights that can enhance early diagnosis and risk stratification in patients with ARDS and sepsis. These findings support the move toward precision medicine, where individualized treatment plans are tailored based on molecular and genetic profiles. Additionally, the review highlights the need for targeted therapeutic interventions that address the specific pathophysiological mechanisms involved in the co-presentation of ARDS and sepsis. These implications underscore the importance of integrating molecular diagnostics and personalized treatment strategies into routine clinical practice to improve patient outcomes.

7. LIMITATIONS

While this review provides a comprehensive synthesis of the current literature on ARDS and sepsis co-presentation, several limitations must be acknowledged. First, the reliance on observational studies introduces inherent biases and limits the ability to establish causal relationships between identified factors and clinical outcomes. Second, the heterogeneity of study designs, patient populations, and methodologies complicates the synthesis of findings and may affect the generalizability of the conclusions drawn. Third, the retrospective application of ARDS phenotype classification models in some studies may introduce selection bias and limit the applicability of these findings to broader patient populations. Lastly, the dynamic nature of critical care medicine means that new evidence may emerge that could alter the current understanding of ARDS and sepsis, necessitating ongoing updates to this review.

8. FUTURE DIRECTIONS OF RESEARCH

Future research should focus on conducting prospective, multicenter studies with standardized methodologies to address the limitations identified in this review. Such studies should aim to validate the molecular phenotypes and biomarkers identified here in larger, more diverse patient populations, with an emphasis on establishing causality and improving generalizability. Additionally, research should explore the integration of molecular diagnostics into clinical practice, assessing the impact of personalized treatment strategies on patient outcomes. Further investigations are also needed to refine therapeutic interventions based on the specific pathophysiological mechanisms underlying ARDS and sepsis, with the goal of reducing mortality and improving the quality of care for these critically ill patients. The development of new biomarkers and genetic tools should be prioritized to enhance early diagnosis, risk stratification, and targeted therapy in this complex clinical scenario.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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