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META-ANALYSIS

Outcomes of acute respiratory distress syndrome in COVID-19 patients compared to the general population: a systematic review and meta-analysis

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ABSTRACT

Introduction: Acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19) often leads to mortality. Outcomes of patients with COVID-19-related ARDS compared to ARDS unrelated to COVID-19 is not well characterized.

Areas covered: We performed a systematic review of PubMed, Scopus, and MedRxiv 11/1/2019 to 3/1/2021, including studies comparing outcomes in COVID-19-related ARDS (COVID-19 group) and ARDS unrelated to COVID-19 (ARDS group). Outcomes investigated were duration of mechanical ventilation-free days, intensive care unit (ICU) length-of-stay (LOS), hospital LOS, and mortality. Random effects models were fit for each outcome measure. Effect sizes were reported as pooled median differences of medians (MDMs), mean differences (MDs), or odds ratios (ORs).

Expert opinion: Ten studies with 2,281 patients met inclusion criteria (COVID-19: 861 [37.7%], ARDS: 1420 [62.3%]). There were no significant differences between the COVID-19 and ARDS groups for median number of mechanical ventilator-free days (MDM: −7.0 [95% CI: −14.8; 0.7], p = 0.075), ICU LOS (MD: 3.1 [95% CI: −5.9; 12.1], p = 0.501), hospital LOS (MD: 2.5 [95% CI: −5.6; 10.7], p = 0.542), or all-cause mortality (OR: 1.25 [95% CI: 0.78; 1.99], p = 0.361). Compared to the general ARDS population, results did not suggest worse outcomes in COVID-19-related ARDS.

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1. Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected over 127.8 million people worldwide, with nearly 2.8 million deaths reported as of 30 March 2021 [1]. While most symptomatic COVID-19 patients have mild flu-like symptoms, approximately 20–30% of patients become critically ill with acute respiratory distress syndrome (ARDS) and severe lung injury requiring mechanical ventilation [2–5]. ARDS is a diffuse, inflammatory-based lung injury linked to various etiologies, including respiratory viral infections. Among patients with COVID-19 admitted to intensive care units (ICU), up to 90% have been reported to develop ARDS, leading to high mortality rates [4]. However, clinical outcome comparisons between ARDS patients with or without COVID-19 diagnosis remain poorly characterized. Here, we systematically reviewed and analyzed the literature of patients with COVID-19 who developed ARDS in order to better understand their characteristics and outcomes compared to the general ARDS population.

2. Methods

2.1. Search protocol

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines [6]. We systematically searched PubMed, Scopus, and MedRxiv between 1 November 2019 and 1 March 2021 using the following search strings: 1) COVID-19 AND acute AND ARDS AND

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(patient OR mortality OR outcomes); 2) COVID-19 AND acute AND ARDs and (patient OR mortality OR ventilation OR discharge) NOT ('case report' OR 'editorial' OR 'letter'); 3) (COVID-19 AND acute AND ARDs and (patient OR mortality OR ventilation OR discharge)) NOT ('case report' OR 'editorial' OR 'letter'); and 4) COVID-19 AND 'acute respiratory distress syndrome' AND (oxygenation OR ventilation OR discharge) AND (predictive OR factors OR prognosis OR manifestations). We also manually reviewed bibliographies of the included studies to retrieve additional relevant articles that were not found during our initial electronic database search. The PRISMA checklist associated with this systematic review can be found in the online Supplementary Information. The protocol of this study was not preregistered with any approved databases of prospectively maintained systematic review protocols (e.g., PROSPERO). Detailed results of our study search, screening, and data extraction process are hosted on the Nested Knowledge website (www.nested-knowledge.com).

2.2. Study selection and risk of bias

We included all studies that reported ARDS in COVID-19 patients within the designated study period. There were no restrictions applied to studies based on patient demographics, such as age, sex, or race. We excluded studies that were not directly relevant to the clinical presentation of ARDS in association with COVID-19, including *in vitro, in vivo*, and *in silico* experimental studies, technical notes, editorials, comments, opinions, studies reporting methods, studies describing qualitative discussion of existing literature, case reports, case series with fewer than five patients, and studies with duplicated datasets or incomplete data. We also excluded studies that did not report outcomes for both ARDS patients with COVID-19 diagnosis and general ARDS patients.

First, the retrieved studies were screened by three independent authors for inclusion (M.S., S.K., and K.M.K.). Then, the included studies were assessed for their quality by using the standardized Joanna Briggs Institute (JBI) critical appraisal instruments for both cohort studies and case series [7,8]. The levels of evidence of individual studies were graded according to the JBI Levels of Evidence for Prognosis [9]. Following previous recommendations [10,11], the risk of bias of individual studies were determined using the following cutoffs: low risk of bias if ≥70% of questions were answered 'yes,' moderate risk if 50–69% questions were answered 'yes,' and high risk of bias if <50% of questions were answered 'yes.'

2.3. Data extraction

Data extraction was performed by three authors (J.R., M.S., and S.K.) and was later checked for accuracy by a different author (J.M.P.). The collected data included publication date, country, study design, and the following clinical outcomes: duration of ventilator-free days, length of ICU stay, hospital length of stay (LOS), and all-cause mortality.

2.4. Statistical analysis

All data were extracted using the Nested Knowledge interface. In some studies, continuous data (e.g., length of ICU stay) were reported as means and standard deviations; however, medians and quantiles were reported in other studies considered for inclusion. In order to compute effect size measures from quantile data, we used methods described by Luo et al. [12] and Wan et al. [13] to estimate means and standard deviations, respectively. Subsequently, individual effect sizes from each study were computed using a homogenous set of summary measures. Data were not transformed when data for a particular outcome measure were strictly reported as medians and quantiles. Data from the Nested Knowledge interface were exported as a .csv file and imported to RStudio (Version 1.3.959, RStudio, PBC, Boston, MA) running on R-4.0.2 for analysis. The 'meta' (Version 4.18–0), 'metafor' (Version 2.4–0), and 'metamedian' (Version 0.1.5) packages were used to perform meta-analyses.

Effect sizes from each study were computed as logarithmically transformed odds ratios (ORs) with random-effects, Mantel-Haenszel weighting for mortality data and as pooled mean differences (MDs) with random-effects, inverse-variance weighting for hospital LOS and length of ICU stay. For comparisons of number of ventilator-free days which were reported as medians and quantiles among all available studies, we computed effect sizes using the weighted median of the difference of medians (MDM) method proposed by McGrath et al. [14]. Logarithmic transformations were used in certain cases to correct for skewed marginal distributions and to shrink the influence of high leverage outliers. To aid in interpretation, logarithmically transformed pooled effect sizes were back-transformed to their original scale.

The between-study variance component of random-effects models were estimated using a restricted effects maximum likelihood (REML) estimator with 95% confidence intervals (CIs) computed using the Q-profile method [15]. 95% prediction intervals (PIs) were also calculated for each outcome measure using methods described by Higgins et al. [16]. In brief, a 95% PI estimates where the true effects are to be expected for 95% of similar (exchangeable) studies that might be conducted in the future. This has a distinct interpretation as compared to 95% CIs, which estimates with 95% probability that the CI will contain the true population mean.

To evaluate heterogeneity between studies, τ^2 statistics (between-study variance component for random-effects models using REML) and Higgin's I^2 statistics (estimated percentage of variability in effect estimates due to heterogeneity rather than sampling error) were computed. Low, moderate, and high between-study variance related to heterogeneity rather than sampling error was indicated by I^2 values of <25%, 25–75%, and >75%, respectively [17]. Forest plots in addition to statistical tests are graphed to present overall effect size and weight of effect measure contributed by individual studies.

3. Results

3.1. Search results

Of the 654 studies retrieved by our database search, 14 studies were included for full-text screening and qualitative synthesis. From these articles, 10 cohort studies comprising data from 2,281 ARDS patients were included in the quantitative meta-analysis (see PRISMA flow diagram in Figure 1). From this patient population, 861 patients (62.3%) had ARDS related to COVID-19 (hereafter, 'COVID-19 group') and 1,420 patients (37.7%) had ARDS related to other causes (hereafter, 'ARDS group'). Among these studies, there were six retrospective studies, three ambidirectional studies, and one prospective cohort study. Study characteristics (including author, date of publication, study type, country, and size) and outcome comparisons between groups for each individual study are shown in Table 1.

3.2. Risk of bias and quality appraisal

Among the 14 studies included for full-text screening, 2 studies were excluded due to outcomes not being separately available for the COVID-19 and ARDS groups. After using the JBI qualitative appraisal checklists for the 12 remaining cohort studies, the majority of studies evaluated in the final quantitative analysis were deemed to be of sufficient quality for inclusion (10/12, 83.3%). According to the JBI risk of bias methods, eight studies were considered to be associated with a low risk of bias and two studies were considered to be associated with a moderate risk of bias. The two excluded studies were considered to be associated with a high risk of bias and low quality of evidence for the purposes of our meta-analysis. Of note, these studies did not provide information on the primary outcomes of interest of our meta-analysis. The results of our quality appraisal are summarized in **Supplementary File 1**.

3.3. Duration of mechanical ventilator-free days

Of the studies included in the quantitative meta-analysis, three studies with 625 patients had sufficient data to evaluate comparisons mechanical ventilator-free days between the COVID-19 and ARDS groups. The pooled median duration of mechanical ventilator-free days in the COVID-19 group was 5.2 days (95% CI = 0; 11.3) compared to 13.0 days (95% CI = 7.5; 18.5) in the ARDS group. The median number of mechanical ventilator-free days was not significantly different between the COVID-19 group and the ARDS group (MDM = −7.0 [95% CI = −14.8; 0.7], p = 0.075; Figure 2). Between-study heterogeneity ranged from moderate to high (I^2 = 83.1% [95% CI = 40.7%; 98.0%], p < 0.001).

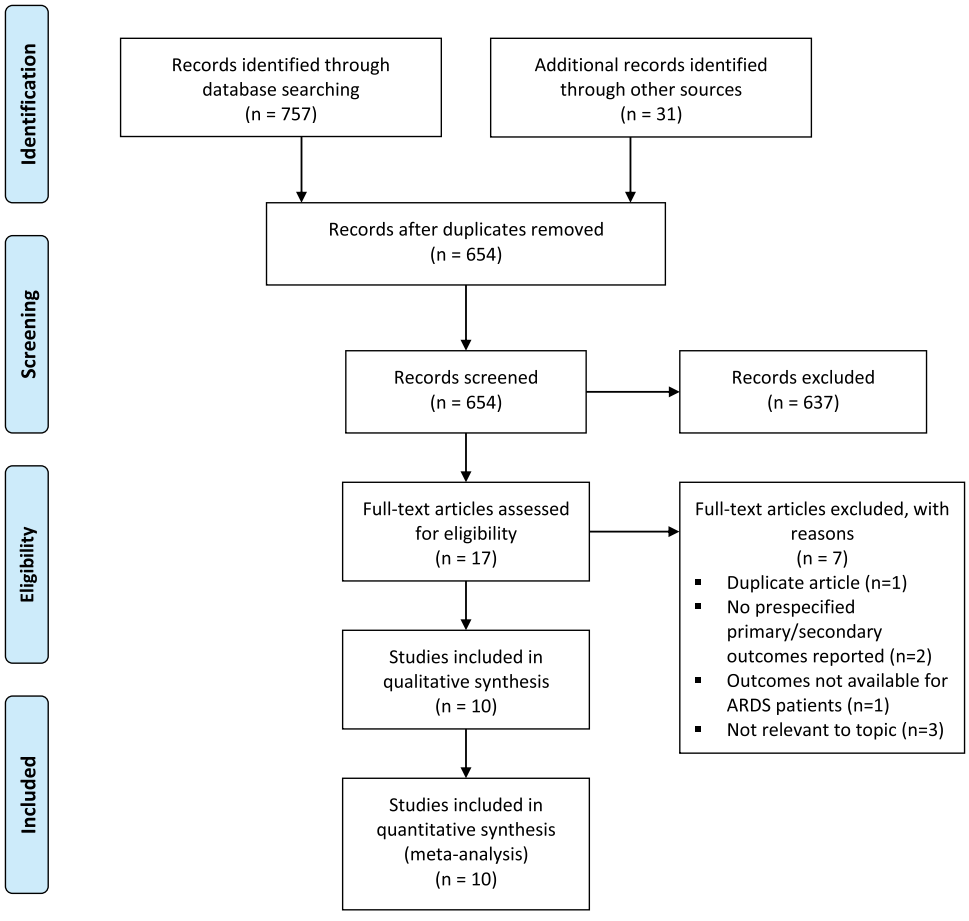

Figure 1. PRISMA diagram of search records and included studies.

Table 1. Study characteristics and outcomes of the included studies.

Study	Ref	Date	Study Type	Country	Arm	N	Mechanical Ventilator-Free Days, Median (IQR)	ICU LOS (days), Mean±SD or Median (IQR)	Hospital LOS (days), Mean±SD or Median (IQR)	Mortality, n (%)
Altınbilek et al.	[18]	8/10/20	R	Turkey	COVID-19	345	.	.	7.7 ± 6.7	46 (13.3%)
					ARDS	495	.	.	4.3 ± 4.8	21 (4.2%)
Bain et al.	[19]	2/5/21	A	USA	COVID-19	27	0 (0–13)	.	.	12 (44.4%)
					ARDS	65	12 (0–23)	.	.	24 (36.9%)
Blot et al.	[20]	11/2/20	PS	France	COVID-19	14	8 (0–15)	.	.	3 (21.4%)
					ARDS	7	18 (17–21)	.	.	1 (14.3%)
Brault et al.	[21]	11/1/20	A	France	COVID-19	24	.	.	.	14 (58.3%)
					ARDS	39	.	.	.	21 (53.8%)
Chiumello et al.	[22]	10/21/20	A	Italy	COVID-19	32	.	13.7 ± 8.1	15 (9–24)	12 (37.5%)
					ARDS	64	.	22.0 ± 13.0	20 (11–33)	29 (45.3%)
Lemmers et al.	[23]	11/16/20	R	Italy	COVID-19	169	.	10 (5–18)	.	86 (50.9%)
					ARDS	163	.	7 (3–20)	.	43 (26.4%)
Lemyze et al.	[24]	5/22/20	R	France	COVID-19	44	.	.	.	10 (22.7%)
					ARDS	39	.	.	.	10 (25.6%)
Luyt et al.	[25]	11/23/20	R	France	COVID-19	50	.	48 (34–68)	.	17 (34.0%)
					ARDS	45	.	30 (20–53)	.	18 (40.0%)
Shah et al.	[26]	5/6/20	R	USA	COVID-19	26	.	8.8 (2.7–17.8)	10.7 (7.9–22.7)	1 (3.8%)
					ARDS	160	.	2.9 (1.6–5.7)	4.7 (2.9–7)	15 (9.4%)
Sjoding et al.	[27]	2/12/21	R	USA	COVID-19	130	9 (0–23)	.	.	39 (30.0%)
					ARDS	382	9 (0–19)	.	.	145 (38.0%)

ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; ICU = intensive care unit; LOS = length of stay; USA = United States of America; IQR = interquartile range; SD = standard deviation; R = retrospective; PS = prospective; A = ambidirectional; Ref = reference.

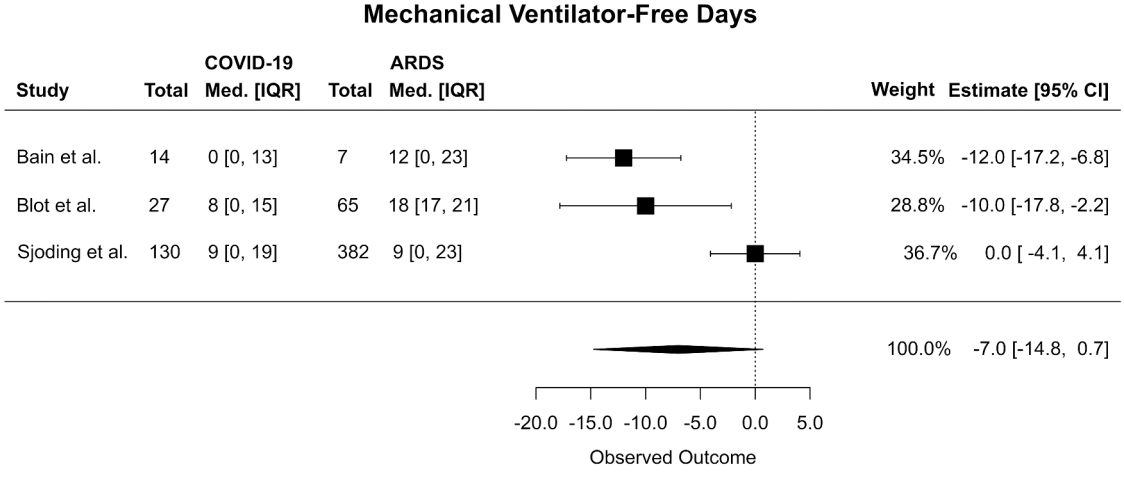

Figure 2. Forest plot of comparisons of duration of mechanical ventilator-free support days. Pooled results were computed using the weighted median of the difference of medians (MDM) method proposed by McGrath et al.

3.4. Length of ICU stay

Of the studies included in the quantitative meta-analysis, four studies with 709 patients had sufficient data to evaluate comparisons of length of ICU stay between the COVID-19 and ARDS groups. The pooled mean length of ICU stay in the COVID-19 group was 16.7 days (95% CI = 7.9; 35.2) compared to 12.7 days (95% CI = 4.7; 34.4) in the ARDS group. There was no significant difference in length of ICU stay between the COVID-19 and ARDS groups (MD = 3.1 [95% CI = −5.9; 12.1], p = 0.501; Figure 3). Between-study heterogeneity was high (I^2 = 92.5% [95% CI = 83.9; 96.5%], $p < 0.001$).

3.5. Length of hospital stay

Of the studies included in the quantitative meta-analysis, three studies with 1,358 patients had sufficient data to evaluate

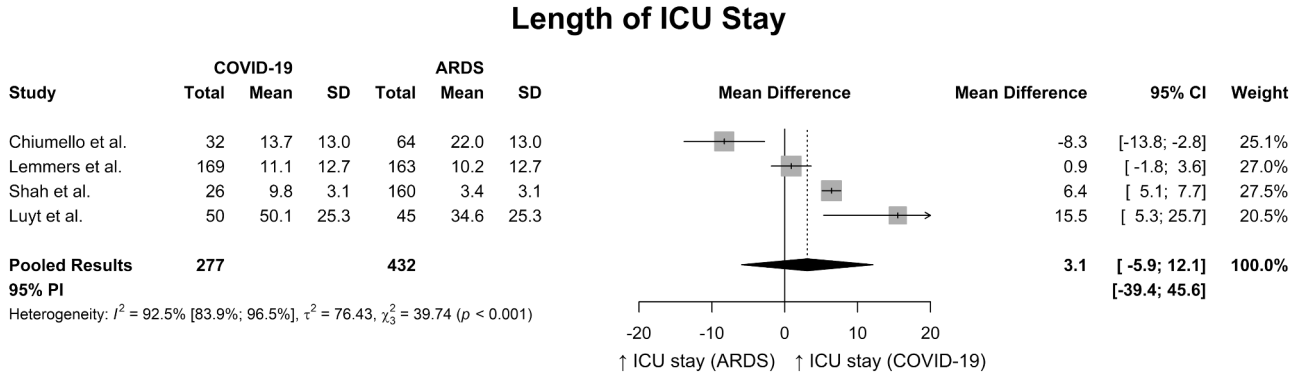

Figure 3. Forest plot of comparisons of length of intensive care unit (ICU) stay (unit = days). Pooled results were computed using restricted effects maximum likelihood with 95% confidence intervals computed using the Q-profile. 95% prediction intervals for the pooled analyses are also displayed.

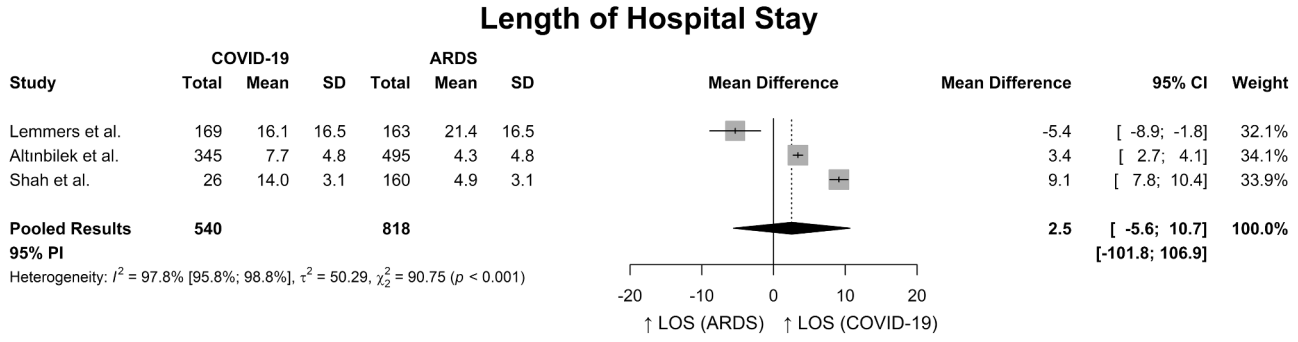

Figure 4. Forest plot of comparisons of length of hospital stay (LOS; unit = days). Pooled results were computed using restricted effects maximum likelihood with 95% confidence intervals computed using the Q-profile. 95% prediction intervals for the pooled analyses are also displayed.

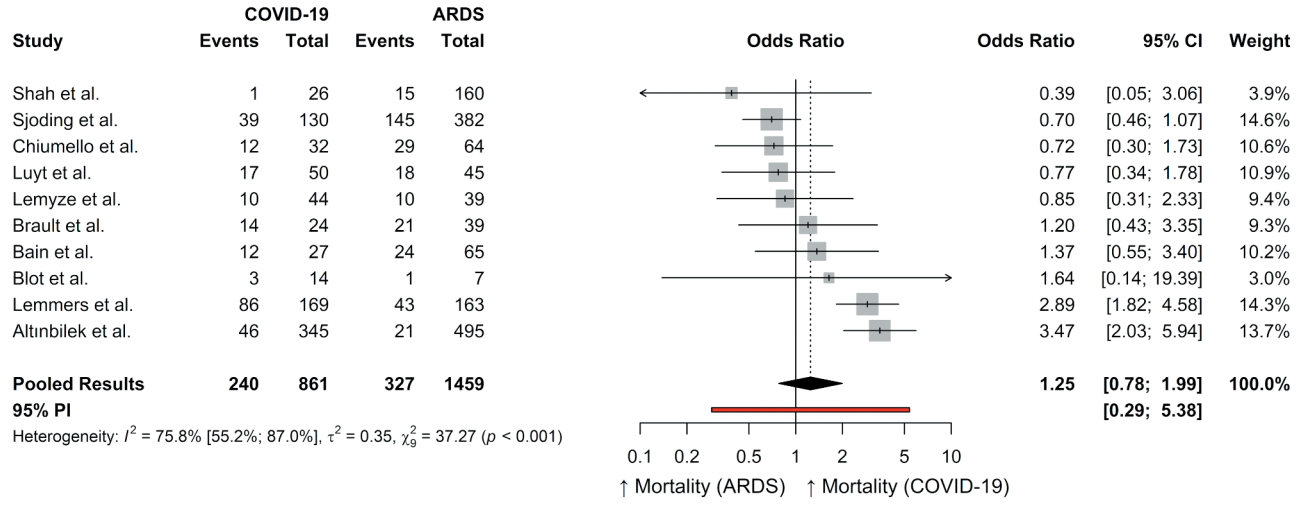

Figure 5. Forest plot of comparisons of all-cause mortality. Pooled results were computed using restricted effects maximum likelihood with 95% confidence intervals computed using the Q-profile. 95% prediction intervals for the pooled analyses are also displayed.

comparisons of hospital LOS between the COVID-19 and ARDS groups. The pooled mean hospital LOS for the COVID-19 group was 11.9 days (95% CI = 7.5; 8.8) compared to 7.7 days (95% CI = 2.8; 21.0) in the ARDS group. There was no significant difference in hospital LOS between the COVID-19 and ARDS groups (MD = 2.5 [95% CI = −5.6; 10.7], $p = 0.542$; Figure 4). Between-study heterogeneity was high (I^2 = 97.8% [95.8%; 98.8%], $p < 0.001$)

3.6. All-cause mortality

All studies included in the quantitative meta-analysis had sufficient data to evaluate the relative odds of all-cause mortality between the COVID-19 and ARDS groups. The overall all-cause mortality rate for the COVID-19 group was 30.9% (95% CI = 21.3%; 42.6%) while the overall mortality rate for the ARDS group was 26.1% (95% CI = 15.5%; 40.6%). There was no significant difference in all-cause mortality between the COVID-19 and ARDS groups (OR = 1.25 [95% CI = 0.78; 1.99], $p = 0.361$; Figure 5). Between-study heterogeneity ranged from moderate to high (I^2 = 75.8% [95% CI = 55.2–87.0%], $p < 0.001$).

4. Discussion

Our meta-analysis of 10 studies, comprising data from 2,281 patients, summarized the most commonly reported outcomes in COVID-19-related ARDS patients compared to ARDS outcomes in the general population. We found no significant differences in duration of mechanical ventilator-free days, length of ICU stay, hospital LOS, or all-cause mortality between the COVID-19 and ARDS groups. The mean predicted all-cause mortality rate among ARDS patients with COVID-19 was similar in comparison to other reported mortality rates in the general ARDS population [28,29]. In light of these findings, it is unlikely that ARDS patients with COVID-19 diagnosis have increased risk of mortality compared to those who have ARDS without COVID-19.

While the etiology of COVID-19-related ARDS is still not understood well, a growing body of evidence suggests that the hyperinflammation seen in COVID-19 ARDS patients is mediated via viral sepsis and kidney, cardiac, and epithelial dysfunction [30,31]. In the general population, ARDS may also be caused by respiratory infections, such as H5N1 avian influenza, or have non-pulmonary pathogenesis, such as septic bacteremia or major trauma [32–34]. Though patients with COVID-19-related ARDS and the general population may have different mechanisms of ARDS onset, the results observed in this meta-analysis suggest that the underlying mechanism of onset may not influence important clinical outcomes like mortality. Interestingly, the respiratory failure and pulmonary edema seen in ARDS is, by definition, non-cardiogenic [35], yet it seems likely that COVID-19-related ARDS involves cardiac injury and dysfunction (among other organ systems) [30,31]. Such an acknowledgment highlights that, in order to better understand the mechanism of severe COVID-19 progression and the etiology of ARDS in these patients, we must be continually aware of and vigilant to the complex interplay that occurs between organ systems.

Outside of the immediately precipitating events leading to ARDS, there are various risk factors and comorbidities associated with the development of ARDS. For patients with a COVID-19 diagnosis, risk factors for ARDS include male sex, hypertension, cardiovascular disease, and cerebrovascular disease [36]. Additionally, a meta-analysis of 45 studies and 4,203 patients by Zhang et al. found that elevated lactate dehydrogenase (LDH) was a significant predictor of ARDS development in patients with COVID-19 [37]. There are conflicting reports of the association between age and COVID-19-related ARDS. Some research has shown that advanced age is associated with increased risk of adverse COVID-19-related ARDS and mortality due to increased prevalence of several comorbidities, such as diabetes and hypertension, as well as dysregulated viral replication secondary to decreased cell-mediated and humoral immunity [38,39]. However, a retrospective cohort study of 5,584 patients at risk of ARDS development found an association between ARDS and decreasing age [40]. In the general population, common risk factors for ARDS include age, chronic alcohol abuse, and smoking; lesser-known risk factors may include environmental exposure to elevated ozone levels and low plasma concentrations of vitamin D [34,41–43]. In this study, the unavailability of patient-level data made it impossible to perform more rigorous analyses with propensity matching and stratification based on patient characteristics and comorbidities. In the future, a meta-analysis that takes advantage of patient-level data would allow for a more sensitive evaluation of outcomes between ARDS patients with or without COVID-19 diagnosis.

5. Expert Opinion

There is no current consensus on the best treatment for ARDS in COVID-19 patients. Generally, the gold standard of ARDS treatment is oxygen support, and several noninvasive and invasive approaches to oxygen therapy have been reported in the COVID-19 patients who develop ARDS [44]. Low tidal volume, high-positive end expiratory pressure (PEEP) mechanical ventilation is well-supported by evidence from the ARDSnet clinical trials [45,46]; however, there is controversy over use of the ARDSnet treatment protocol in the setting of COVID-19 due to altered hemodynamics [47,48]. Since patient outcomes were typically not stratified by type of ventilation support, we were not able to make inferences about best supportive measures for COVID-19-related ARDS. Other non-pharmacological interventions for COVID-19 ARDS patients include placing them in prone position, which reduces lung strain and typically results in markedly improved oxygenation and arterial blood gases [49]. Long-term treatments of ARDS, such as pulmonary rehabilitation for movement-related fatigue, were not within the scope of this study, but would provide valuable research insights for COVID-19-related ARDS survivors.

COVID-19 patients with ARDS may also be supported by medications. Although the literature on pharmacological management of COVID-19 patients with ARDS has been limited [50], results from the RECOVERY trial (NCT04381936) published in February 2021 suggest that corticosteroid treatment with dexamethasone can reduce 28-day mortality among COVID-19 patients requiring invasive mechanical ventilation or oxygen support [51]. While this does not specifically speak to the

efficacy of dexamethasone in COVID-19 patients with ARDS, this corticosteroid treatment regimen may improve the severely compromised respiration that ARDS patients experience. Immunosuppressive drugs such as IL-1 blockers (e.g., anakinra) and therapeutic monoclonal antibodies (e.g., eculizumab) have also been identified as potential future therapies; however, each of these drugs are expensive and are only hypothesized to be efficacious based on mechanism of action, and there is no clinical evidence to support their therapeutic potential for COVID-19-related ARDS [50]. Time and additional research will shed light on the efficacy of these and other potential pharmacological therapies, especially as new variants of SARS-CoV-2 emerge.

Limitations of this review include variable follow-up periods and lack of validated and objective measurement of clinical parameters, such as disease severity. Although the research question underlying this study necessarily precludes randomized controlled trials from consideration, it must be acknowledged that our evidence base of primarily observational/retrospective studies is also a limitation. Few studies included outcome data specifically for the ARDS population, making inferences from this target population impossible; as such, our patient population and included studies are relatively small, which is another weakness. In addition, most studies included in the meta-analysis did not report cause of death, limiting our pooled analysis to all-cause mortality. Our analysis was primarily composed of in-hospital and short-term clinical outcomes; further research is required to understand the long-term consequences of ARDS secondary to COVID-19. Among the included studies, outcome data was rarely stratified by treatment interventions, preventing us from evaluating the relative efficacy among common treatments. Though beyond the scope of the current study, future studies would benefit from complex, multivariable prediction models that take such differences in patient populations and treatment methods into account.

5. Conclusion

ARDS is a common complication of COVID-19 associated with a high risk of mortality and poor clinical outcome. Compared to the general ARDS population observed in the literature, our results did not suggest increased risk of mortality or worse outcomes for patients with COVID-19-related ARDS.

Reviewer disclosures

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Declaration of interest

NLR, SK, JR, AB, MS, DS, and KC work for Nested Knowledge and Superior Medical Experts. KWE, GP, ARD, and MA. JCT is employed by and has ownership interest in Superior Medical Experts. KMK works for and holds equity in Nested Knowledge and Superior Medical Experts. JMP is employed by and has ownership interest in Nested Knowledge and Superior Medical Experts. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Data availability statement

Additional data not contained in the article is available upon reasonable request.

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