Higher Risk of Acute Respiratory Distress Syndrome and Risk Factors among Patients with COVID-19: A Systematic Review, Meta-Analysis and Meta-Regression

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Abstract: Objective: To estimate the global risk and risk factors associated with acute respiratory distress syndrome (ARDS) among patients with COVID-19: Design: A systematic review, meta-analysis and meta-regression. Setting and Participants: Hospitals or nursing homes and patients with acute respiratory distress syndrome after COVID-19. Methods: The literature review was systematically conducted on Embase, MEDLINE, CINAHL, and Web of Science, in addition to manual searches and reference list checking from 1 January 2019 to 2 March 2022. The search terms included coronavirus, acute respiratory syndrome, acute respiratory distress syndrome and observational studies. Three reviewers independently appraised the quality of the studies and extracted the relevant data using the Joanna Briggs Institute abstraction form and critical appraisal tools. A study protocol was registered in PROSPERO (CRD42022311957). Eligible studies were meta-analyzed and underwent meta-regression. Results: A total of 12 studies were included, with 148,080 participants. The risk ratio (RR) of ARDS was 23%. Risk factors were age ≥ 41–64 years old (RR = 15.3%, 95% CI = 0.14–2.92, p = 0.03); fever (RR = 10.3%, 95% CI = 0.03–2.03, p = 0.04); multilobe involvement of the chest (RR = 33.5%, 95% CI = 0.35–6.36, p = 0.02); lymphopenia (RR = 25.9%, 95% CI = 1.11–4.08, p = 0.01); mechanical ventilation with oxygen therapy (RR = 31.7%, 95% CI = 1.10–5.25, p = 0.002); European region (RR = 16.3%, 95% CI = 0.09–3.17, p = 0.03); sample size ≤ 500 (RR = 18.0%, 95% CI = 0.70–2.89, p = 0.001). Conclusions and Implications: One in four patients experienced ARDS after having COVID-19. The age group 41–64 years old and the European region were high-risk groups. These findings can be used by policymakers to allocate resources for respiratory care facilities and can also provide scientific evidence in the design of protocols to manage COVID-19 worldwide.

Keywords: acute respiratory distress syndrome; coronavirus infection; risk factor

1. Introduction
The novel coronavirus disease 2019 (COVID-19) is associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and severe acute respiratory syndrome (SARS), which caused the global pandemic of COVID-19 in late 2019 and which is continuing to date [1–3]. The rapid increase in COVID-19 has critically influenced society, healthcare systems, and people worldwide [4,5]. The clinical spectrum of disease presentation could be asymptomatic, mild, moderate, or severe, with some cases leading to death. In addition, some patients develop severe lung failure (acute respiratory distress syndrome, ARDS) [3,6,7]. Previous research data showed that 76-40% of cases in Greece [8] and 61.7%
in Germany [9] have developed ARDS in high proportions. However, data also show lower rates of 3.60% in Poland [10], and the admission rate to intensive care units (ICU) is 11.5%, as high as in [11]. It is also evident that patients with moderate-to-severe ARDS need invasive mechanical ventilation and a wide range of therapeutic actions [10,12].

Furthermore, patients who recovered after ARDS may have a decline in exercise capacity and health-related quality of life [10]. Previous literature showed that 30% of hospital admissions among COVID-19 patients experienced ARDS [13], and some among them had experienced the insertion of extracorporeal membrane oxygenation (ECMO) after COVID-19 [14]. They understand the global risk of ARDS among patients with COVID-19 to allocate resources and other healthcare management of post-recovery ARDS patients with COVID-19. Furthermore, some research studies found that age, sex, and previous illness history, such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, asthma, and chronic kidney failure, may influence the incidence of ARDS among patients with COVID-19 [15–18]. However, no studies have systematically included all risk factors. Moreover, no systematic review and meta-analysis studies were conducted using the primary research data to describe the risk of ARDS and risk factors among patients having COVID-19 from a global perspective. Therefore, this study aims to identify the global risk and the risk factors associated with acute respiratory distress syndrome among patients with COVID-19.

1.1. The Objective of This Study

This study aimed to estimate the global risk and risk factors associated with acute respiratory distress syndrome among patients with coronavirus infection.

1.2. Research Question

What are the global risk and risk factors associated with acute respiratory distress syndrome among patients with coronavirus infection?

2. Methods

2.1. Search Strategy

This study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO Reg No—CRD42022311957). Five databases (Embase, MEDLINE, CINAHL, and Web of Science) were searched for studies on the prevalence of acute respiratory distress syndrome among patients with coronavirus published between 1 January 2019 and 2 March 2022. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) were followed [19–22]. English synonyms including coronavirus, acute respiratory disease, 2019-nCoV, COVID-19, SARS-CoV, respiratory syndrome, severe acute respiratory syndrome, severe acute respiratory infection, Middle East respiratory syndrome, hospital, hospitalization, hospitalized, inpatient, patient, and sufferer were used to search each database. Several control vocabularies for the Emtree and MeSH databases were also used. For Emtree, these included “coronavirus”, “Wuhan seafood market pneumonia virus”, “Wuhan coronavirus”, “Hospital patient”, “Adult respiratory distress syndrome”, “severe acute respiratory syndrome”, “ARDS”, and “SARS”. We supplemented the search results with the Endnote X9 bibliographical database. Publications that cited the papers identified during the search and the reference lists of relevant articles and previous systematic reviews were manually screened to confirm the sensitivity of the search strategy.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria were: (1) the study provided primary data on the prevalence of acute respiratory distress syndrome (ARDS) measured using validated assessment tools or coded medical report data within a population-based study after COVID-19 occurred; (2) participants were diagnosed with COVID-19; and (3) the studies were observational, such as cohort and cross-sectional studies, and were published in English, Chinese, or
Sinhala from 2019 to 2022. The following types of studies were excluded: studies for which the study population did not include COVID-19 patients and studies that were qualitative research and review articles.

Titles and abstracts were independently screened by three researchers based on the inclusion and exclusion criteria after removing duplicates using the Endnote X9 bibliographic database. Then, the full texts of the selected studies were reviewed by three researchers independently, with any disagreement resolved by a fourth researcher to avoid selection bias.

2.3. Quality Assessment

All eligible studies were assessed for quality of evidence using the Joanna Briggs Institute (J.B.I.) Critical Appraisal for Checklist for Prevalence Studies Scale (CACPSS), which contains nine items and four responses (yes, no, unclear, and not applicable) [23]. Studies with a total score of 8 and above were considered acceptable quality evidence and were included in this systematic review and meta-analysis. Study quality and risk of bias were also independently assessed by the three reviewers, with any disagreement resolved by a fourth researcher.

2.4. Data Extraction

The following data were extracted: names of authors, year of publication, country, settings, study design, sample size, participant ethnicity, age, gender, and prevalence of acute respiratory distress syndrome. In addition, three authors independently assigned quality scores for the included studies according to the PRISMA guidelines [20–22], and any disagreements were resolved via a discussion among all four authors.

2.5. Statistical Analysis

A meta-analysis was conducted to identify statistical outcomes of higher risk of ARDS among patients with COVID-19 using the eligible studies. The pooled prevalence of acute respiratory distress syndrome was analyzed using several events converted to the risk ratio of 95% CI and p-values and a fitted model based on heterogeneity. Random or fixed-effects models were used based on the heterogeneity of results for acute respiratory distress syndrome among coronavirus infection patients. We transformed the proportions with the Freeman–Tukey double arcsine method before pooling the data for the prevalence rate of acute respiratory distress syndrome [24]. The heterogeneity value was assessed using I², Cochran’s Q test, and Tau2 for the included studies according to the DerSimonian–Laird estimator [25–28]. A zero value indicated the absence of heterogeneity, 25% indicated no significance or low significance, 50% indicated moderate heterogeneity, and 75% indicated significant heterogeneity. In the present study, 75–100% indicated significant heterogeneity, where the Q statistic and p-value were used to validate the heterogeneity results. In this meta-analysis, I² < 75% and p < 0.05 indicated statistical significance.

Publication bias was determined using funnel plots, and the Q statistic for Egger’s test was used to determine the correlation between the effect estimate and the variances in the results for acute respiratory distress syndrome via C.M.A. software and a visual examination of the funnel plots [29,30]. A subgroup analysis and a meta-regression were performed to investigate potential sources of heterogeneity. For the meta-regression, we used the pool of effect size data as a single covariable introduced individually into the models. A simultaneous test was conducted to determine if all coefficients were zero in the model test. We used a null hypothesis model for the effect size comparison. Statistical analyses were conducted using Comprehensive Meta-Analysis Software version 3.0 (Biostat, Englewood, NJ, USA.) [23].
3. Results

3.1. Study Identification

A total of 35,005 articles published from 1 January 2019 to 2 March 2022 were identified during the initial database search. Six thousand seven hundred eighty-seven articles were removed as duplicates using the Endnote X9 bibliographical database. The titles and abstracts of 28,220 articles were screened, and 1611 articles met the inclusion criteria. The full text of each article was read to determine eligibility, and 1596 articles were excluded due to the following reasons: 469 articles did not have any relationship to COVID; 1099 articles did not mention ARDS behaviour among COVID-19 patients; 25 articles did not assess the outcome variables; and 3 articles were not available in a full-text format. In addition, three articles were removed after the quality assessment due to a low-quality score in the peer review. Finally, 12 articles were included in the systematic review and meta-regression (Figure 1). Studies with quality scores of 8 and above were accepted as high quality (Supplementary Table S1).

3.2. Study Characteristics

Characteristics of the 12 included studies are shown in Table 1. The included studies were conducted in 7 countries. Four were conducted in China [31–34], two were in the United States [15,35] and Germany [3,9], and only one was from Greece [8], India [36], Poland [10], and Korea [37]. Regarding the study design used, six were retrospective studies [10,15,31,33–35], three were cross-sectional studies [3,8,9], two were cohort studies [32,37], and one was a prospective study [36]. Regarding the study setting, 12 studies were conducted in a hospital. These studies were published between 2020 and 2022 (Table 1).
Table 1. Characteristics of the included studies.

| Author, (Year) | Country | WHO Region                      | Study Design          | Ethnicity (n)                      | Mean Age | Sample Size (n) | Gender (n)       | Prevalence Rate of ARDS (n) (%) | Joanna Briggs Institute Score |
|----------------|---------|---------------------------------|-----------------------|-----------------------------------|----------|----------------|-----------------|---------------------------------|-----------------------------|
| Dreher et al. (2020) | Germany [3] | European region                  | Cross-sectional study | Caucasian: 50                      | ALL: 65. | 50             | Male—33 | 24 (48%)                        | 9                           |
|                 |         |                                 |                       | ARDS: 62. No ARDS: 68.            |          |                | Female—17 |                                    |                             |
| Wang et al. (2020) | China [31] | Western Pacific region            | Retrospective study   | Chinese: 130                       | ALL: 45. | 130            | Male—17 | 26 (20%)                        | 9                           |
| Wu et al. (2020)  | China [32] | Western Pacific region            | Cohort study          | Chinese: 201                       | ALL: 69  | 201            | Female—128 | 84 (41.80%)                      | 8                           |
| El-Solh et al. (2021) | United States [35] | Region of the Americas         | Retrospective study   | Caucasian: 3547                    | ALL: 45. | 7816           | Male—7387 | 643 (8.23%)                      | 9                           |
|                 |         |                                 |                       | ARDS: 58. No ARDS: 42.            |          |                | Female—60 |                                    |                             |
| Hu et al. (2021)  | China [34] | Western Pacific region            | Retrospective study   | Chinese: 197                       | ALL: 45. | 197            | Male—93  | 13 (6.60%)                        | 9                           |
|                 |         |                                 |                       | ARDS: 58. No ARDS: 42.            |          |                | Female—104 |                                    |                             |
| Mizera et al. (2021) | Germany [9] | European region                  | Cross-sectional study | Caucasian: 60                      | ALL: 45. | 60             | Male—36  | 37 (61.67%)                      | 8                           |
| Sehgal et al. (2021) | India [36] | South-East Asian region           | Prospective study     | Chinese: 68                        | NA       | 68             | Female—24 | 23 (33.82%)                      | 9                           |
| Seo et al. (2021)  | Korea [37] | Western Pacific region            | Cohort study          | Korean: 166                        | ARDS: 72. | 166            | Male—78  | 37 (22.29%)                      | 8                           |
|                 |         |                                 |                       | African: 4089                      | No ARDS: 56 |                | Female—88 |                                    |                             |
|                 |         |                                 |                       | Caucasian: 7462                    |          |                |                | 258 (21.85%)                      | 8                           |
| Singhal et al. (2021) | United States [15] | Region of the Americas         | Retrospective study   | Indian: 258                        | ARDS: 62. | 14,785         | Male—7358 | 2052 (13.88%)                    | 8                           |
|                 |         |                                 |                       | Asian: 427                        | No ARDS: 68. |                | Female—7427 |                                    |                             |
|                 |         |                                 |                       | Mixed race: 4                       |          |                |                | 2544 (0.17%)                      |                             |
| Vassiliou et al. (2021) | Greece [8] | European Region                  | Cross-sectional study | Caucasian: 89                      | ARDS: 62. | 89             | Male—70  | 68 (76.40%)                      | 9                           |
| Xu et al. (2021)  | China [33] | Western Pacific region            | Retrospective study   | Chinese: 659                       | ARDS: 56. | 659            | Female—19 | 76 (11.53%)                      | 9                           |
| Gujski et al. (2022) | Poland [10] | European Region                  | Retrospective study   | Caucasian: 116,539                 | NA       | 116,539        | Male—60,915 | 4237 (3.60%)                     | 9                           |
|                 |         |                                 |                       |                                    |          |                | Female—55,624 |                                    |                             |
3.3. Participant Characteristics

The total participants in the 12 studies were 148,080 individuals; 74,385 were male, and 72,860 were female. The participant age range in 12 studies was 30–70 years of age, and one study [36] did not mention the participant’s age.

In terms of ethnicity, five studies were conducted using Chinese populations [32–34,36,38], five studies were conducted in Caucasian populations [3,8–10,35], and one study from the United States also mentioned five ethnic groups (African American, Caucasian, American Indian, Asian, Mixed) [15]. One study was conducted in a Korean population [37]. Studies were conducted in 4 WHO regions: five studies were conducted in the Western Pacific region [31–34,37], four studies were conducted in the European region [3,8–10], two studies were conducted in the region of the Americas [15,35], and one study was conducted in the South-East Asian region [36] (Table 1).

3.4. Higher Risk of ARDS among Patients with COVID-19

Within the seven countries (the United States, Germany, Greece, India, China, Poland, and Korea), 12 studies analyzed the higher risk of acute respiratory distress syndrome among patients with COVID-19. The reported numbers were 7320 of 140760 participants, and four studies in the European region showed the highest rates of ARDS (Tables 1 and 2). After conducting a meta-analysis, we found that the pooled risk ratio of ARDS among patients with COVID-19 was 23% (95% CI = 14.3–34.7%, \( p = 0.001 \)), with significant heterogeneity within the 12 studies (\( I^2 = 99.70 \), \( Q = 3685.601 \), Tau2 = 1.002, \( p = 0.001 \), Figure 2).

Figure 2. Prevalence rate of acute respiratory distress syndrome (ARDS) in patients with COVID-19 [3,8–10,15,31–37].
Table 2. Meta-analysis according to subgroup and meta-regression used to identify factors affecting heterogeneity within the selected studies.

| Variable                        | No of Study | Sample | Risk Ratio (%) (95% CI) | p-Value | I² | Coefficient | Standardized Error | 95% CI     | p-Value |
|--------------------------------|-------------|--------|-------------------------|---------|----|-------------|-------------------|------------|---------|
| Gender                         | 12          | 147711 | 23.8 (17.7–31.2)        | 0.001   | 99.42 | Reference   |                    |            |         |
| Female                         | 12          | 72860  | 22.8 (14.5–33.9)        | 0.001   | 99.05 | Reference   |                    |            |         |
| Male                           | 12          | 74851  | 25.1 (14.7–39.4)        | 0.001   | 99.60 | 0.1048      | 0.4521           | −0.78–0.99 | 0.8166  |
| Age                            | 5           | 138642 | 10.0 (6.2–15.7)         | 0.001   | 99.66 | Reference   |                    |            |         |
| 14–40 years old                | 5           | 3,642  | 12.4 (2.6–42.3)         | 0.001   | 99.61 | Reference   |                    |            |         |
| ≥65 years old                  | 3           | 49793  | 4.4 (2.6–7.3)           | 0.001   | 95.37 | 1.5309      | 0.8132           | −0.45–2.73 | 0.1618  |
| Smoking                        | 4           | 9498   | 14.1 (9.4–20.5)         | 0.001   | 95.37 | Reference   |                    |            |         |
| No smoking                     | 4           | 5587   | 15.5 (6.8–31.5)         | 0.001   | 97.49 | Reference   |                    |            |         |
| Smoking                        | 4           | 3911   | 12.5 (5.5–25.7)         | 0.008   | 79.48 | −0.2463     | 0.7439           | −1.70–1.21 | 0.7406  |
| Cluster exposure history       | 2           | 735    | 15.9 (8.7–27.4)         | 0.001   | 85.31 | Reference   |                    |            |         |
| No exposure history            | 2           | 277    | 16.8 (12.8–21.7)        | 0.290   | 10.68 | Reference   |                    |            |         |
| Fever                          | 7           | 10139  | 14.8 (9.9–21.7)         | 0.001   | 96.16 | Reference   |                    |            |         |
| No fever                       | 7           | 4404   | 8.5 (4.7–15.1)          | 0.001   | 73.26 | Reference   |                    |            |         |
| Fever                          | 7           | 5735   | 20.9 (12.0–33.7)        | 0.001   | 97.09 | Reference   |                    |            |         |
| Muscular soreness              | 3           | 1022   | 11.5 (6.8–18.8)         | 0.001   | 83.12 | Reference   |                    |            |         |
| No muscular soreness           | 3           | 842    | 13.8 (6.6–26.5)         | 0.001   | 91.80 | Reference   |                    |            |         |
| Muscular soreness              | 3           | 180    | 8.7 (5.3–14.0)          | 0.438   | 0.00 | −0.5387     | 0.6182           | −1.75–0.67 | 0.3835  |
| Cough                          | 7           | 10029  | 22.2 (15.2–31.3)        | 0.001   | 96.51 | Reference   |                    |            |         |
| No cough                       | 7           | 7010   | 18.0 (9.2–32.1)         | 0.001   | 93.50 | Reference   |                    |            |         |
| Cough                          | 7           | 3019   | 26.8 (15.6–42.1)        | 0.001   | 96.50 | 0.5185      | 0.5164           | −0.49–1.53 | 0.3153  |
| Productive cough               | 5           | 1317   | 19.3 (12.5–28.5)        | 0.001   | 91.20 | Reference   |                    |            |         |
| No productive cough            | 5           | 775    | 16.6 (8.7–29.6)         | 0.001   | 91.86 | Reference   |                    |            |         |
| Productive cough               | 5           | 542    | 22.1 (11.3–38.7)        | 0.001   | 91.72 | 0.3575      | 0.5552           | −0.73–1.44 | 0.5196  |
Table 2. Cont.

| Variable                        | No of Study | Sample  | Risk Ratio (%) (95% CI) | p-Value | $I^2$  | Coefficient | Standardized Error | 95% CI          | p-Value |
|---------------------------------|-------------|---------|-------------------------|---------|-------|-------------|--------------------|-----------------|---------|
| No sore throat                  | 4           | 957     | 17.3 (8.9–31.0)         | 0.001   | 92.93 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| Sore throat                     | 4           | 133     | 10.0 (5.9–16.7)         | 0.654   | 0.00  | −0.7391     | 1.9171             | 1.0015          | −0.45–3.88 | 0.0556  |
| No dyspnea                      | 4           | 6097    | 8.6 (2.9–22.8)          | 0.001   | 95.91 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| Dyspnea                         | 4           | 2947    | 38.5 (11.4–75.4)        | 0.001   | 98.04 | 1.0015      | 0.6484             | −2.01–0.53      | 0.2543  |
| Fatigue                         | 3           | 8381    | 9.1 (7.2–11.4)          | 0.001   | 76.35 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| No fatigue                      | 3           | 6787    | 10.1 (9.4–10.9)         | 0.182   | 41.29 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| Fatigue                         | 3           | 1594    | 8.6 (5.2–13.9)          | 0.010   | 78.34 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| Headache                        | 3           | 1029    | 20.3 (11.0–34.5)        | 0.001   | 89.51 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| No headache                     | 3           | 876     | 19.6 (10.0–34.9)        | 0.001   | 91.03 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| Headache                        | 3           | 153     | 23.0 (3.5–71.4)         | 0.001   | 92.12 | 1.0015      | 0.6484             | −2.01–0.53      | 0.2543  |
| Diarrhea                        | 6           | 9854    | 14.7 (10.5–20.0)        | 0.001   | 90.32 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| No diarrhea                     | 6           | 8936    | 14.9 (9.2–23.2)         | 0.001   | 94.83 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| Diarrhea                        | 6           | 918     | 11.1 (9.1–13.5)         | 0.018   | 63.50 | −0.0371     | 0.4417             | −0.90–0.82      | 0.9330  |
| Nausea and vomiting             | 3           | 1022    | 13.6 (8.7–20.5)         | 0.001   | 77.02 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| No nausea and vomiting          | 3           | 912     | 12.2 (6.8–20.9)         | 0.001   | 87.59 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| Nausea and vomiting             | 3           | 110     | 16.3 (6.6–35.0)         | 0.088   | 58.81 | 0.3524      | 0.5670             | −0.75–1.46      | 0.5342  |
| Lung infiltrates or consolidation| 3           | 460     | 14.7 (4.9–36.9)         | 0.001   | 90.59 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| No lung infiltrates or consolidation| 3          | 225     | 6.9 (4.1–11.1)          | 0.066   | 0.00  | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| Lung infiltrates or consolidation occurred | 3         | 235     | 24.7 (6.0–62.9)         | 0.001   | 91.70 | 0.4722      | 1.0722             | 1.0015          | −0.45–3.88 | 0.0556  |
| Multilobe involvement in chest  | 2           | 366     | 7.3 (1.6–28.1)          | 0.001   | 90.70 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| Without multilobe involvement in chest| 2        | 116     | 0.8 (0.1–5.8)           | 0.986   | 0.00  | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| With multilobe involvement in chest| 2         | 250     | 19.7 (4.3–75.2)         | 0.001   | 95.14 | 1.5330      | 3.3557             | 0.35–6.36       | 0.0286  |
| Leucopenia                      | 2           | 327     | 14.9 (7.1–28.6)         | 0.003   | 78.69 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| Without leucopenia              | 2           | 83      | 18.1 (11.2–27.9)        | 0.714   | 0.00  | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| With leucopenia                 | 2           | 244     | 12.4 (3.1–39.0)         | 0.001   | 91.60 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
| Lymphopenia                     | 2           | 327     | 11.1 (2.6–37.4)         | 0.001   | 93.32 | Reference   | 0.6484             | −2.01–0.53      | 0.2543  |
Table 2. Cont.

| Variable                                      | Meta-Analysis | Meta-Regression |
|-----------------------------------------------|---------------|-----------------|
|                                               | No of Study   | Sample          | Risk Ratio (%) (95% CI) | p-Value | I² | Coefficient | Standardized Error | 95% CI | p-Value |
| Without lymphopenia                           | 2             | 227             | 3.1 (1.5–6.4)     | 0.614    |    |             | Reference           |        |         |
| With lymphopenia                              | 2             | 100             | 30.4 (12.2–5.8)   | 0.011    | 84.47 |             | 2.5987             | 0.7571 | 1.11–4.08 | 0.0006 |
| Underlying medical illnesses                  | 4             | 1103            | 32.7 (15.8–55.8)  | 0.001    | 95.48 |             | Reference           |        |         |
| Without underlying medical illnesses          | 4             | 593             | 34.6 (10.5–70.6)  | 0.001    | 95.34 |             | Reference           |        |         |
| With underlying medical illnesses             | 4             | 510             | 31.2 (9.3–66.6)   | 0.001    | 95.99 | -0.1561     | 1.0793             | -2.27–1.95 | 0.8850 |
| Diabetes mellitus                             | 10            | 131086          | 22.7 (16.3–30.6)  | 0.001    | 98.69 |             | Reference           |        |         |
| Without diabetes mellitus                     | 10            | 119438          | 17.8 (10.0–29.4)  | 0.001    | 98.97 |             | Reference           |        |         |
| With diabetes mellitus                        | 10            | 11648           | 29.9 (18.9–43.8)  | 0.001    | 96.92 | 0.7022      | 0.4680             | -0.21–1.61 | 0.1335 |
| Hypertension                                  | 10            | 131100          | 20.6 (14.9–27.7)  | 0.001    | 98.68 |             | Reference           |        |         |
| Without hypertension                          | 10            | 111673          | 15.2 (8.5–25.9)   | 0.001    | 98.34 |             | Reference           |        |         |
| With hypertension                             | 10            | 19427           | 28.5 (16.5–44.5)  | 0.001    | 98.59 | 0.7917      | 0.4925             | -0.17–1.75 | 0.1079 |
| Chronic obstructive pulmonary disease         | 8             | 130591          | 20.8 (14.1–29.7)  | 0.001    | 98.53 |             | Reference           |        |         |
| Without chronic obstructive pulmonary disease | 8             | 125717          | 19.4 (11.0–32.0)  | 0.001    | 99.15 |             | Reference           |        |         |
| With chronic obstructive pulmonary disease    | 8             | 4874            | 21.4 (12.0–35.3)  | 0.001    | 89.10 | 0.3264      | 0.5407             | -0.73–1.38 | 0.5461 |
| Asthma                                        | 3             | 777             | 25.4 (12.6–44.4)  | 0.001    | 84.17 |             | Reference           |        |         |
| Without asthma                                | 3             | 766             | 19.4 (8.8–37.6)   | 0.001    | 90.94 |             | Reference           |        |         |
| With asthma                                   | 3             | 11              | 49.1 (18.7–80.2)  | 0.317    | 12.85 | 1.3206      | 0.9398             | -0.52–3.16 | 0.1600 |
| Chronic kidney failure                        | 8             | 131013          | 20.0 (13.8–28.3)  | 0.001    | 98.48 |             | Reference           |        |         |
| Without chronic kidney failure                | 8             | 125421          | 19.9 (11.7–31.9)  | 0.001    | 99.16 |             | Reference           |        |         |
| With chronic kidney failure                   | 8             | 5592            | 19.1 (10.6–31.8)  | 0.739    | 91.53 | 0.1008      | 0.5133             | -0.90–1.10 | 0.8443 |
| Chronic cardiac disease                       | 7             | 130816          | 13.1 (9.3–18.2)   | 0.001    | 98.86 |             | Reference           |        |         |
| Without chronic cardiac disease               | 7             | 99673           | 13.0 (6.5–24.3)   | 0.001    | 99.39 |             | Reference           |        |         |
| With chronic cardiac disease                  | 7             | 31143           | 11.2 (7.1–17.2)   | 0.048    | 92.89 | 0.1858      | 0.5377             | -0.86–1.23 | 0.7296 |
| Coronary artery disease                       | 3             | 258             | 43.6 (25.4–63.7)  | 0.001    | 83.69 |             | Reference           |        |         |
| Without coronary artery disease               | 3             | 235             | 34.5 (16.9–57.8)  | 0.001    | 90.22 |             | Reference           |        |         |
| With coronary artery disease                  | 3             | 23              | 62.4 (35.3–83.4)  | 0.262    | 25.28 | 1.1040      | 0.8250             | -0.51–2.72 | 0.1808 |
| Thyroid disease                               | 2             | 247             | 25.5 (19.5–32.2)  | 0.159    | 42.11 |             | Reference           |        |         |
| Without thyroid disease                       | 2             | 236             | 26.0 (16.1–39.2)  | 0.073    | 68.96 |             | Reference           |        |         |
| With thyroid disease                          | 2             | 11              | 32.0 (8.5–70.5)   | 0.179    | 44.66 | 0.2440      | 0.9489             | -1.61–2.10 | 0.7971 |
| Antiviral therapy                             | 2             | 398             | 24.0 (7.4–55.3)   | 0.001    | 94.74 |             | Reference           |        |         |
| Variable                                      | No of Study | Sample | Risk Ratio (%) (95% CI) | p-Value | $I^2$ | Coefficient | Standardized Error | 95% CI       | p-Value |
|----------------------------------------------|-------------|--------|-------------------------|---------|------|-------------|--------------------|-------------|---------|
| Without antiviral therapy                    | 2           | 331    | 35.6 (4.9–85.6)         | 0.001   | 93.64 | Reference   |                     |             |         |
| With antiviral therapy                       | 2           | 67     | 15.4 (1.6–66.6)         | 0.001   | 97.38 | −1.1104     | 1.7311             | −4.50–2.28  | 0.5212  |
| Antibiotic therapy                           | 2           | 495    | 15.0 (3.5–46.3)         | 0.001   | 94.37 | Reference   |                     |             |         |
| Without antibiotic therapy                   | 2           | 144    | 7.8 (2.9–19.0)          | 0.255   | 22.77 | Reference   |                     |             |         |
| With antibiotic therapy                      | 2           | 351    | 20.3 (2.8–68.9)         | 0.001   | 95.14 | 0.8311      | 1.5353             | −2.17–3.84  | 0.5883  |
| Nasal cannula oxygen therapy                 | 2           | 398    | 20.1 (4.6–56.7)         | 0.001   | 96.64 | −1.1104     | 1.7311             | −4.50–2.28  | 0.5212  |
| Without nasal cannula oxygen therapy         | 2           | 139    | 42.9 (10.7–82.5)        | 0.001   | 94.20 | Reference   |                     |             |         |
| With nasal cannula oxygen therapy            | 2           | 259    | 7.8 (1.3–34.9)          | 0.001   | 92.14 | −2.1811     | 1.3269             | −4.78–0.41  | 0.1002  |
| Mechanical ventilation oxygen therapy        | 4           | 15272  | 47.0 (19.1–76.9)        | 0.001   | 99.69 | −1.1104     | 1.7311             | −4.50–2.28  | 0.5212  |
| Without mechanical ventilation oxygen therapy| 4           | 13425  | 17.4 (5.3–44.3)         | 0.001   | 98.63 | Reference   |                     |             |         |

**Table 2. Cont.**

| Variable                                      | No of Study | Sample | Risk Ratio (%) (95% CI) | p-Value | $I^2$ | Coefficient | Standardized Error | 95% CI       | p-Value |
|----------------------------------------------|-------------|--------|-------------------------|---------|------|-------------|--------------------|-------------|---------|
| WHO region                                    | 12          | 148080 | 83.9 (48.3–96.7)        | 0.001   | 87.16| 3.1785      | 1.0584             | 1.10–5.25   | 0.0027  |
| Region of the Americas                        | 2           | 25296  | 10.7 (6.3–17.6)         | 0.001   | 99.34| Reference   |                     |             |         |
| European region                               | 4           | 121104 | 39.3 (4.2–90.5)         | 0.001   | 99.53| 1.6336      | 0.7856             | 0.09–3.17   | 0.0376  |
| Western Pacific region                         | 5           | 1589   | 18.0 (9.1–32.4)         | 0.001   | 96.10| 0.6010      | 0.7562             | −0.88–2.08  | 0.4268  |
| Southeast Asian region                         | 1           | 91     | 33.8 (23.6–45.8)        | 1.00    | 0.00 | 1.4473      | 1.1285             | −0.76–3.65  | 0.1997  |
| Sample size                                    | 12          | 148080 | 23.0 (14.3–34.7)        | 0.001   | 99.70| Reference   |                     |             |         |
| >500                                          | 4           | 146807 | 8.4 (3.7–18.1)          | 0.088   | 99.89| Reference   |                     |             |         |
| ≤500                                          | 8           | 1273   | 35.7 (21.3–53.2)        | 0.001   | 95.33| 1.8006      | 0.5585             | 0.70–2.89   | 0.0013  |

CI, confidence interval.
3.5. Risk Factors of ARDS among COVID-19 through Meta-Regression Analysis

Based on the meta-analysis results, we identified significant heterogeneity within outcome variables of risk of ARDS. Therefore, a meta-regression analysis was conducted to identify factors affecting heterogeneity through the subgroups. The meta-regression model included the following risk factors for ARDS among patients with COVID-19: gender, age, smoking, cluster exposure history, fever, muscular soreness, cough, productive cough, sore throat, dyspnea, fatigue, headache, diarrhea, nausea and vomiting, lung infiltrates or consolidation, multilobe involvement in the chest, leucopenia, lymphopenia, underlying illnesses, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, asthma, chronic kidney failure, chronic cardiac disease, coronary artery disease, thyroid disease, antiviral therapy, antibiotic therapy, nasal cannula oxygen therapy, mechanical ventilation oxygen therapy, WHO region, and sample size. The results regarding acute respiratory distress syndrome among coronavirus infection patients for statistical model 1, random effects, Z-distribution, and the log odds ratio. The model test was a simultaneous test to confirm that all coefficients (excluding the intercept) were zero (Q = 3685.601, df = 12, p = 0.00). The following risk factors were identified as having a significant relationship with ARDS for patients with coronavirus infection: age greater than or equal to 41–64 years old (RR = 15.3%, 95% CI = 0.14–2.92, p = 0.03); fever (RR = 10.3%, 95% CI = 0.03–2.03, p = 0.04); multilobe involvement in the chest (RR = 33.5%, 95% CI = 0.35–6.36, p = 0.02); lymphopenia (RR = 25.9%, 95% CI = 1.11–4.08, p = 0.01); mechanical ventilation with oxygen therapy (RR = 31.7%, 95% CI = 1.10–5.25, p = 0.002); European region (RR = 16.3%, 95% CI = 0.09–3.17, p = 0.03); and sample size less than or equal to 500 (RR = 18.0%, 95% CI = 0.70–2.89, p = 0.001) (Table 2).

3.6. Publication Bias

Publication bias was analyzed using a funnel plot and Egger’s test on ARDS among patients with COVID-19 for the 12 studies. However, the funnel plot did not show evidence of asymmetry, and there was a minor probability of publication bias. Statistically, possible publication bias was observed based on Egger’s test results (Q = 3685.6, p = 0.001, I² = 99.70%). Figure 3 due to the diversity of the sample sizes and the length of the publication time in the included studies.

![Figure 3. Funnel plots describing publication bias based on ARDS in patients with COVID-19.](image-url)
4. Discussion

This systematic review and meta-analysis evaluated the higher risk of ARDS among patients with COVID-19 during the recent pandemic of COVID-19. A comprehensive search for relevant studies yielded 12 studies from 7 countries across the four WHO regions (region of the Americas, the Southeast Asian region, the European region, and the Western Pacific region) from 2020 to 2022. Additionally, this study has identified risk factors for ARDS among patients with COVID-19 to provide scientific evidence for respective stakeholders to prepare and allocate resources for any future pandemics.

According to our findings, 23% of COVID-19 patients experienced ARDS. This means that nearly one in four patients had progressed to ARDS. Those who had COVID-19 needed to have advanced care plans for further treatments because severe respiratory failure with the progress of ARDS is a possible complication of COVID-19 infection. Additionally, it may relate to the cause of death in COVID-19. Therefore, well-organized and reliable observational systems are beneficial for the patient screening process to detect ARDS early among patients with COVID-19, especially in people in residential care facilities. This will aid in early transfer to specialized medical care units for the proper management of ARDS to minimize the risk of death and severe complications, such as lung fibrosis or permanent lung damage. Most importantly, the early identification of high-risk patients will be the better choice for timely, evidence-based treatments and approaches to prevent further post-COVID-19 complications [9,15,35,37].

Furthermore, this study analyzed possible risk factors associated with ARDS in COVID-19 patients. Age greater than or equal to 41–64 years was a significant risk factor for ARDS among patients with COVID-19. Our results were consistent with previous studies, with similar significant factors associated with the poor prognosis of COVID-19 [34,38–40]. In addition, as per previous literature, medical co-mobilities were associated with the risk of ARDS in middle-aged adults who had COVID-19, specifically pre-existing respiratory disease. However, we did not find any significant association between medical co-morbidities and ARDS [3,40]. Therefore, a pre-preparedness lifestyle modification strategy needs to be applied for future prevention plans for COVID-19 for middle-aged adults around the globe. An example of this would be effective communication for information distribution during pandemics within adult communities to mitigate their myths about infectious diseases such as COVID-19 in the future [41,42].

According to our analysis, fever, multilobe involvement in the chest, lymphopenia, and mechanical ventilation with oxygen therapy were significant clinical risk factors for ARDS among patients with COVID-19. This is because most respiratory distress patients need multifaceted ventilation systems and frequent position changes, such as prone positioning and vital sign monitoring. Therefore, clinicians and healthcare people need to arrange facilities for a long-time inpatient care management strategy for their clinical units [9,15,31,32]. It should be more suitable for nursing home care facilities to arrange respiratory care resources for a future convention.

4.1. Strengths

This study has several strengths. First, we have included studies from four WHO regions with different populations and ethnicities, such as black, white, Chinese, and Indian. This was the first systematic review and meta-regression for ARDS among patients with COVID-19 to include risk factors. Therefore, we recommend future studies should include the Eastern Mediterranean region with Arabic and Islamic populations and the African region with the black African community to see if there is any difference in risk of ARDS and risk factors. This is because, in our findings, the European region is one of the significant risk factors for ARDS among patients with COVID-19 [3,8,9]. In our study, when to start mechanical ventilation and how mechanical ventilation processes proceeded during the clinical management were also found to be risk factors for ARDS. Therefore, it is essential to identify the oxygenation peak flow measurement during ventilation periods, such as from the starting point until the end. Additionally, continuous blood saturation monitoring and
advanced technological methods for blood oxygenation, such as extracorporeal membrane oxygenation (ECMO), are recommended [3,14,43–45].

4.2. Limitations

There were some limitations to our study. First, we noticed a possible publication bias due to the diversity of the sample sizes and the length of the publication time in the included studies. Therefore, we need to include a large sample with long-term observational studies, such as prospective cohort studies, throughout the pandemic. At this time, the available published studies were limited to 12 within seven countries due to early publication. Future analysis can be focused more on studies with new treatment strategies, such as ECMO, for ARDS and their survival rate. Most of the patients in the included studies are still in the hospital under treatment. Therefore, post-COVID co-morbidity for ARDS among patients with COVID-19 need to be analyzed in the future rehabilitation of patients with ARDS.

5. Conclusions

One in four patients has a risk of ARDS after acquiring COVID-19. The risk factors included middle-aged adults older than or equal to 41–64 years old, fever, multilobe involvement in the chest, lymphopenia, and mechanical ventilation with oxygen therapy. Additionally, the European region is at a high risk of ARDs among COVID-19 patients. Therefore, this study’s findings are beneficial for frontline clinicians, healthcare clinical decision-makers, and health policymakers to precisely justify the healthcare system and government of COVID-19 to arrange early interventions and suitable treatment strategies.

This study provides scientific evidence to support clinical practice and the design of protocols to prevent ARDS. It is also a reference for future researchers who plan to examine ARDS and the risk factors among diverse populations. We recommend that future studies focus on the Eastern Mediterranean and African regions with multiple co-morbidities.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph192215125/s1, Table S1. The Joanna Briggs Institute score for quality of evidence for prevalence studies.

Author Contributions: Y.-T.T. and H.-C.K. conceptualized the study and developed the research protocol. Y.-T.T., H.-C.K., N.-Y.K. and L.-F.C. identified articles for the full-text review. Y.-T.T., H.-C.K., S.D.M. and Y.-J.T. extracted data from the studies that matched the inclusion criteria. Y.-T.T., N.-Y.K. and S.P.K.M. performed the statistical analyses. Y.-T.T., S.P.K.M., H.-C.K., L.-F.C., S.D.M., N.-Y.K. and Y.-J.T. contributed to the writing of the manuscript. All authors have read and agreed to the published version of the manuscript.

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