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Acute Respiratory Distress Syndrome and COVID-19: A Scoping Review and Meta-analysis

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Abstract

Acute respiratory distress syndrome (ARDS) is a fatal complication of the new severe acute respiratory syndrome coronavirus (SARS-CoV-2), which causes COVID-19 disease. This scoping review was carried out with international, peer-reviewed research studies and gray literature published up to July 2020 in Persian and English languages. Using keywords derived from MESH, databases including Magiran, IranMedex, SID, Web of Sciences, PubMed, Embase via Ovid, Science Direct, and Google Scholar were searched. After screening titles and abstracts, the full texts of selected articles were evaluated, and those which passed the criteria were analyzed and synthesized with inductive thematic analysis.

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Study quality was also evaluated using a standard tool. The overall prevalence of ARDS was estimated using a random-effects model. This led to identification of 23 primary studies involving 2880 COVID-19 patients. All articles were observational with a cross-sectional, retrospective, case report, and cohort design with moderate to strong quality. The main findings showed that COVID-19-related ARDS has a high prevalence and is different to ARDS due to other etiologies. Elderly and patients with comorbidities and organ failure should be closely surveyed for respiratory organ indications for several weeks after the onset of respiratory symptoms. There is currently no definitive treatment for ARDS in COVID-19 disease, and supportive therapies and their effects are somewhat controversial.

Keywords

Covid-19 · Acute respiratory distress syndrome (ARDS) · Scoping review · Meta-analysis

18.1 Introduction

In December 2019, the world was faced with the sudden outbreak of the SARS-CoV-2 virus which causes COVID-19 disease and was deemed a substantial threat to worldwide health by the World Health Organization (WHO) [1–3]. By March 6, 2020, more than 100,000 persons in 93 countries had been infected by SARS-CoV-2, and this rapidly progressed to over 12 million persons in 213 countries and territories by July 10, 2020 (Fig. 18.1) [4]. Clinical manifestations caused by the virus have varied from fever, cough, fatigue, sputum production, shortness of breath, sore throat, headache, gastrointestinal symptoms like diarrhea and vomiting, as well as acute respiratory distress syndrome (ARDS) and organ failure [5, 6]. Compared to other organs, the COVID-19 virus appears to most affect the respiratory system in the initial stages and in some patients develops to ARDS [7]. Although ARDS patients receive respiratory and therapeutic support in the intensive care unit (ICU), these patients still show a high mortality [8].

According to the Berlin definition, ARDS is a type of acute diffuse, inflammatory lung injury, which can lead to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue [9]. The clinical manifestations are hypoxemia, bilateral opacities in computed tomography (CT) imaging, increased venous admixture, and physiological dead space. One way of measuring this is to determine the ratio of the arterial partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2). Based on the degree of hypoxemia, ARDS can be classified as mild (PaO_2/FIO_2: >200 – ≤300 mm Hg), moderate (>100 – ≤200), or severe (<100) [9]. In the most severe cases, inspired oxygen cannot reach the blood circulation, leading to organ failure and death of the patient (Fig. 18.2).

Some previous review studies have estimated the prevalence of ARDS as 14–28% in COVID-19 patients [10, 11]. Given the critical impact of ARDS on patient outcomes and the current lack of effective treatment options, we have carried out a scoping review and meta-analysis to systematically assess its prevalence in COVID-19 patients. It was also of interest to identify clinical features that could be used to predict or monitor disease severity as a means of informing treatment options.

18.2 Methods

This scoping review study was conducted systematically according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12–15]. A flowchart of the study selection procedure is shown in Fig. 18.3.

18.2.1 Search Strategy

In this review, any original studies conducted worldwide and published in the English or Persian languages in internal and external databases were evaluated up to July 2020. To search for ARDS and COVID-19 studies, we employed the national databases including Magiran, IranMedex, Iranian Archive for Scientific Documents Center (IASD),

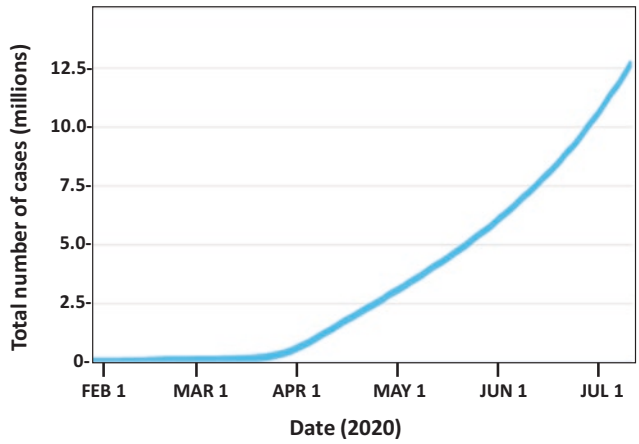

Fig. 18.1 Total number of COVID-19 cases globally from the end of January to July 10, 2020

and Iranian National Library (INL) and international databases such as MEDLINE (PubMed, Ovid), Scopus, Web of Science, Embase, ProQuest, Google, and Google Scholar. Gray literature and reference lists of the extracted primary articles were also reviewed to discover potential related studies. The keywords and subject headings used to search for these databases are shown in Table 18.1. These were used separately and in combination as a syntax using Boolean operators such as "AND," "OR," "NOT," and the "*" sign.

18.2.2 Study Selection Process

The inclusion and exclusion criteria for selecting primary articles are indicated in Table 18.2. Firstly all feasible studies were recognized. Secondly, the titles and abstracts of the identified articles were separately screened by two investigators, and the full texts of relevant articles were obtained and their eligibility was determined. In case of disagreement between the two researchers, the article in question was reviewed by an additional author who was an expert in review studies.

18.2.3 Quality Assessment and Data Extraction

To evaluate the quality of the studies, five-item tools were used, as described in previous studies [16–19]. The five items were related to the research design, sampling method, sample size, comparison group, and psychometric properties. Each item scaled from 0 to 3 and the overall score was from 0 to 15 [17]. Based on this approach, the studies were divided into three categories related to quality, which were defined as either weak (score 4 or below), medium (score 5 to 10), or strong (score above 10). The assessment was performed by two authors (MJO and FRB), and the disagreements were resolved by the senior author (AVA). A data extraction form was used to assemble the information in each article as follows: first author, year of study conduction, design and purpose of the study, setting, main findings and conclusions, limitations, and language. To guarantee accuracy, two other authors examined the extracted data for the final review.

18.2.4 Synthesis of Data and Analysis

Inductive thematic analysis was performed using the results of preliminary studies to find potentially important emerging themes [20]. The results of each of these studies were assessed and compared until the primary themes were outlined. To estimate the overall ARDS prevalence, each study was assessed using calculations of the binary distribution variance. Weighted averages were used to combine the prevalence values of the studies. The weight assigned to each study was an inverse of its vari-

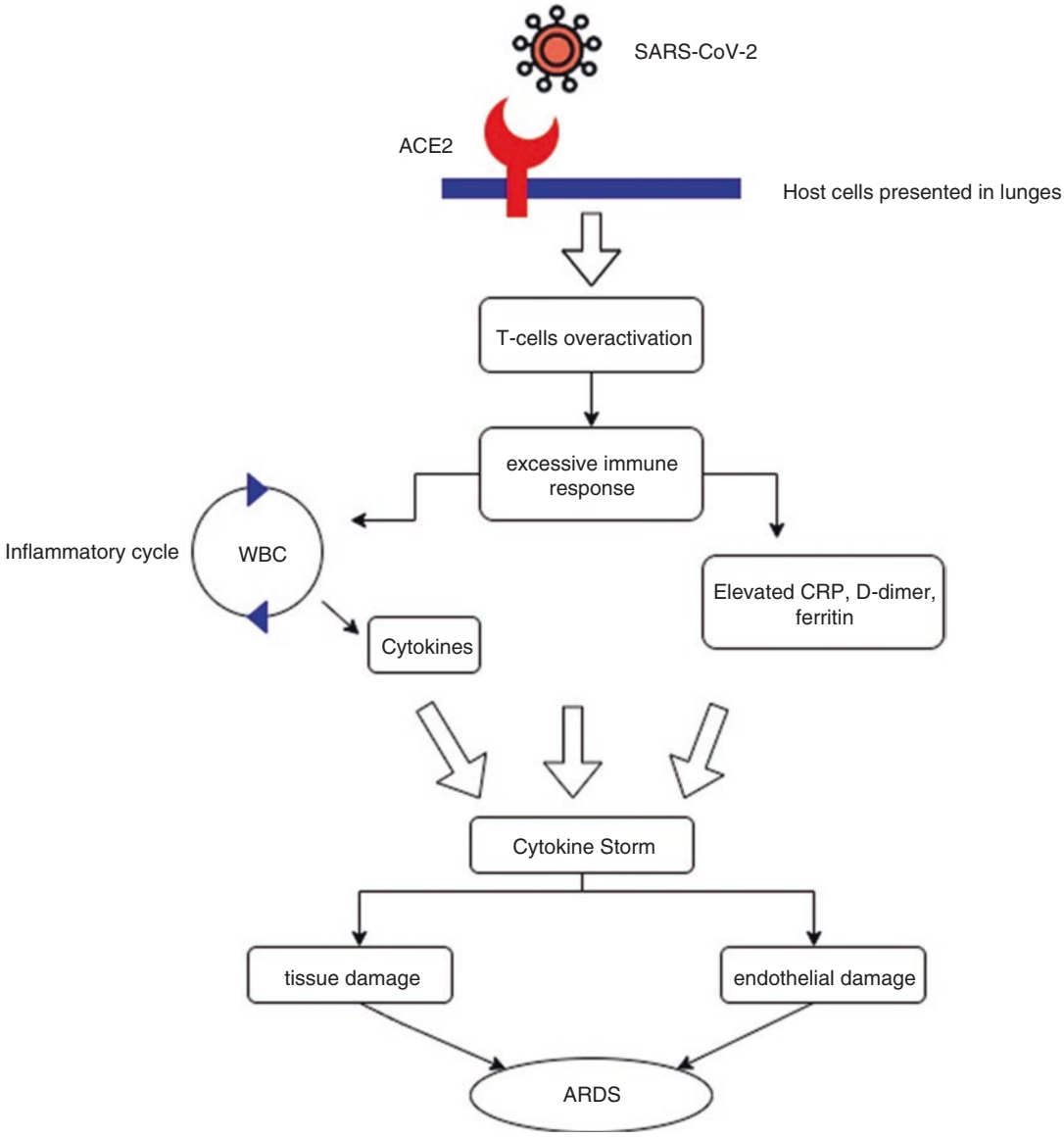

Fig. 18.2 The effects of ARDS on breathing in COVID-19 disease

ance. The heterogeneity of the studies was assessed by the I^2 index. Data heterogeneity was divided into three classes of less than 25% (low heterogeneity), 25 to 75% (medium heterogeneity), and more than 75% (high heterogeneity). Due to the resulting high heterogeneity of the data in this review, a random-effects model was applied. The analysis was conducted with STATA 12 software (StataCorp LLC; College Station, TX, USA).

18.3 Results

18.3.1 Literature Search

The flowchart of the selection process is revealed in Fig. 18.3. A total of 1100 potential study references were acquired after searching the database and search engines and the pertinent reference lists. After the first screening of titles and abstracts, 95 studies were selected to assess the

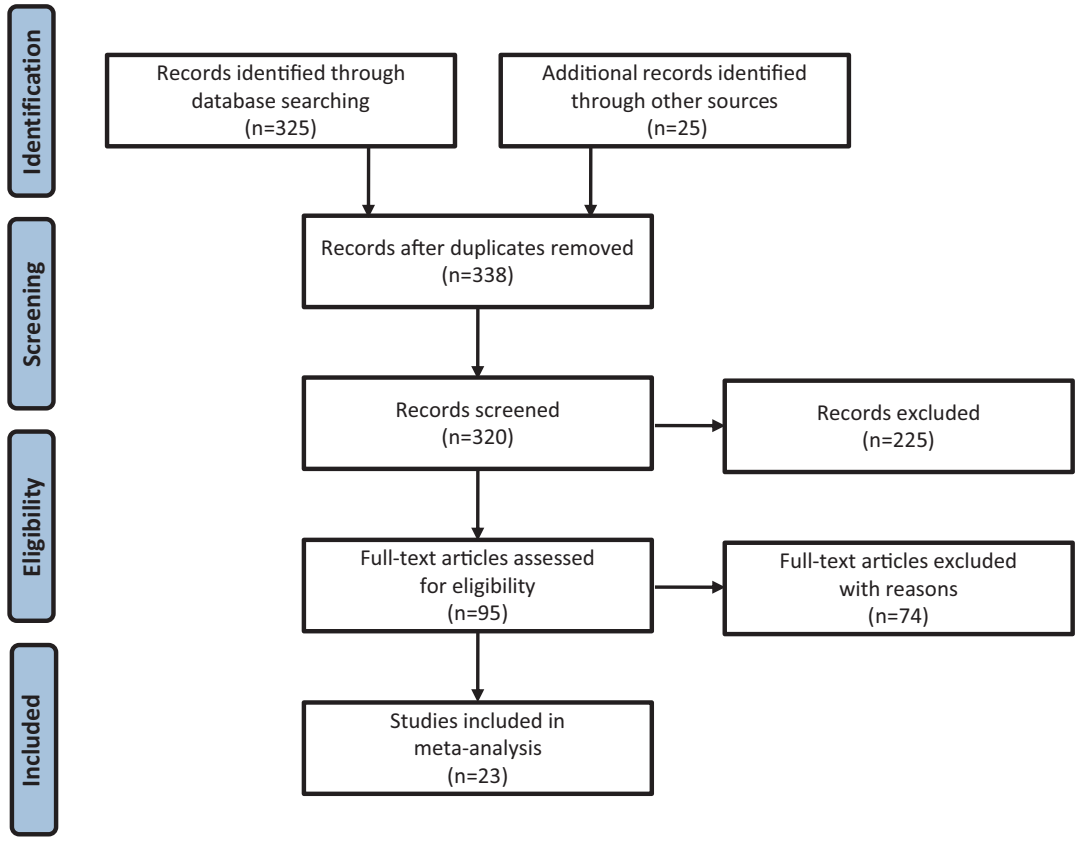

Fig. 18.3 Identification and selection of studies

Table 18.1 Keywords and subject headings used during the search

Search terms
"lung recruitment maneuver" OR "recruitment manoeuver" OR "lung volume recruitment" OR "lung recruitment" OR "recruit manoeuver" OR "recruit manoeuver" OR "recruit manoeuver" OR "recruit manoeuver" OR "PEEP setting" OR "recruitment ARDS" "titrated PEEP" OR "PEEP titration" OR "low PEEP" OR "protective lung strategy" OR "high PEEP" OR ards OR "acute respiratory distress" OR "acute chest syndrome" OR "respiratory distress syndrome" OR "shock lung" OR "adult respiratory distress syndrome" OR "respiratory distress syndrome, acute" AND "Novel coronavirus" OR "Novel coronavirus 2019" OR "2019 novel coronavirus" OR "2019 nCoV" OR "Wuhan coronavirus" OR "Wuhan pneumonia" OR Covid-19 OR "2019-nCoV" OR "SARS-CoV-2" OR "coronavirus 2019" OR "2019-nCoV"

Table 18.2 Inclusion and exclusion criteria for selected primary articles

Inclusion criteria	Exclusion criteria
Peer-reviewed, primary studies	Not peer-reviewed, primary research
Published in English or Persian	Not written in English or Persian
Pointing to the ARDS on patients with Covid-19	Not related to the empirical data (letters, editorials, news, etc.)
Published until July 2020	Low-quality studies Studies that did not include the keywords of "ARDS," "coronavirus 2019," or "Covid-19"

Table 18.3 Characteristics of the primary articles

No.	Author	Year	Design	Sample size	Country	Data type	Aim of the study	Main findings	Conclusion	Limitations	Quality score
1	Chu et al. [21]	2003	Cohort	133 patients with confirmed SARS	China	RT-PCR	N/A	Incidence of ARDS: 32 (24.1%). Risk factors: ARDS: age (p =0.001), comorbidity (p=0.002), initial LDH (p=0.034), and qPCR result of nasopharyngeal specimen (ps=0.025)	N/A	Limited to two centers	Strong
2	Albarello et al. [22]	2020	Case report	Two COVID-19 patients	Italy	X-ray and CT imaging	Present imaging findings of first two patients identified in Italy with COVID-19 infection traveling from Wuhan, China	Moderate to severe lung infiltrates, in bilateral and multi-segmental extension of lung opacities. Follow-up: tubular and enlarged appearance of pulmonary vessels with sudden caliber reduction and mediastinal lymphadenopathy on day 4 ARDS	Pulmonary vessel enlargement is early radiological sign of lung impairment	Low sample size and short time interval for follow-up CT	Medium
3	Beerkenset al. [23]	2020	Case report	21-year-old man with sickle cell disease	USA	Single-cell RNA sequencing in blood and urine	COVID-19 causing acute chest syndrome	On HD 5: atelectasis in the right lower lung. On HD 11: diffuse GGOs and reticular opacities	N/A	N/A	Medium
4	Chen et al. [24]	2020	RCT retrospective	44 patients with H7N9 in control and 17 in intervention group	China	Laboratory and imaging findings	Assessing effect of mesenchymal stem cell transplant on treatment of COVID-19-related ARDS	Intervention: transplantation of mesenchymal stem cells (MSCs) Results: mortality in intervention group < control group and without harmful effects	MSCs can be used in treatment of COVID-19-related ARDS	Low sample size	Strong
5	Yang et al. [25]	2020	Single-centered, retrospective, observational	52 critically ill adult patients with COVID-19 pneumonia	China	Demographic, symptoms, laboratory values, comorbidities, treatments, clinical outcomes	Comparing clinical manifestation of survivors and non-survivors	Survivors: ARDS in 9 patients Non-survivors: ARDS in 26 patients Mortality rate of patients with ARDS: 61.5%	Survival time of non-survivors likely to be within 1–2 weeks after ICU admission. ARDS: increased risk of death	Low sample size	Medium
6	Xu et al. [26]	2020	Retrospective case report	A 50-year-old with COVID-19	China	Laboratory test results, chest CT scans	Assessing pathogenesis of COVID-19	Symptoms: fever, chills, cough, fatigue, and shortness of breath.	N/A	N/A	Strong

								Chest X-ray: multiple patchy shadows in both lungs, progressive infiltrate and diffuse gridding shadow in both lungs. HD 13: oxygen saturation >95%.			
								HD14: oxygen saturation 60% and sudden cardiac arrest. Lung biopsy samples: bilateral diffuse alveolar damage with cellular fibromyxoid exudates. Right lung showed evident desquamation of pneumocystis and hyaline membrane formation, indicating ARDS. Left lung: pulmonary edema with hyaline membrane formation suggesting early-phase ARDS.			
								Treatment: corticosteroids, ventilator support, interferon alpha-2b, moxifloxacin			
7	Wu et al. [27]	2020	Retrospective cohort	201 patients with confirmed COVID-19 pneumonia	China	Epidemiology, demographics, clinical, laboratory, management, treatment, and outcome data	Describe clinical characteristics and outcomes in patients with COVID-19 pneumonia who developed ASRS or died	84 patients developed ARDS, and of these patients, 44 died. Patients with ARDS had more dyspnea, hypertension, and diabetes than patients without ARDS. Older age, neutrophilia, and organ and coagulation dysfunction were risk factors associated with development of ARDS and progression from ARDS to death. Among patients with ARDS, treatment with methylprednisolone decreased risk of death	Older age greater risk of ARDS and death. High fever associated with ARDS and better outcomes. Treatment with methylpre dnisolone may be beneficial for patients who develop ARDS	Only patients with severe COVID-19 pneumonia Single hospital with limited sample size, selection bias when identifying factors that influence clinical outcomes	Strong
8	Wang et al. [28]	2020	Cross-sectional	339 elderly patients with COVID-19	China	Demographics, clinical features, comorbidities, laboratory tests and complications	To investigate characteristics and prognostic factors in elderly patients with COVID-19	ARDS: 21% comorbidities including cardiovascular disease, and COPD and ARDS were strong predictors of death	N/A	Only one hospital	Strong

(continued)

Table 18.3 (continued)

No.	Author	Year	Design	Sample size	Country	Data type	Aim of the study	Main findings	Conclusion	Limitations	Quality score
9	Wang et al. [29]	2020	Case series	Three cases with COVID-19 and ARDS (75-year-old male, 59-year-old female, and 49-year-old)	China	N/A	Tissue plasminogen activator (tPA) treatment for COVID-19-associated ARDS	Case 1: hydroxychloroquine and azithromycin given for 5 days. tPA given intravenously over 2 h, followed by infusion over subsequent 22 h. 11 h into tPA infusion the P/F ratio improved to 408, a twofold improvement from pre-tPA. By HD 11: multiple organ failure with refractory hypotension secondary to arrhythmia and superimposed bacterial infection and died.	tPA: in all three cases, patients demonstrated initial improvement in their P/F ratio, with improvements ranging from a 38% improvement (case 3) to a ~100% improvement (Case 1). The improvements were transient in all three patients. Formal studies needed to determine whether this resulted from tPA therapy or due to unrelated /random effects	N/A	Medium
								Case 2: oxygen requirement progressed over 2 days from nasal cannula O2 to a 100% mask with a PaO2 of 137. On HD 4 patient required intubation. Vasopressor for hemodynamic support. IVtPA administered as intravenous bolus over 2 h, followed by infusion over subsequent 22 h.			
								Case 3: Same as case 2			

10	Tang et al. [30]	2020	Retrospective case control	Patients with either COVID-19 (n=73) or H1N1 (n=75) with ARDS	China	N/A	Explore different clinical presentations between COVID-19 and influenza A (H1N1) pneumonia in patients with ARDS	P/F ratio of 198.2 mmHg in COVID-19 patients significantly higher than the P/F ratio of 107.0 mmHg of H1N1 patients ($p<0.001$). GGOs more common in COVID-19 patients than in H1N1 patients ($p<0.001$)	Many differences between COVID-19 and H1N1-induced ARDS patients	Condition of H1N1 patients more severe than that of COVID-19 patients	Strong
11	Shi et al. [31]	2020	Cohort	416 hospitalized patients with COVID-19	China	Clinical laboratory, radiological, and treatment data	Explore association between cardiac injury and mortality in COVID-19 patients	97 patients had ARDS	N/A	Data from larger populations and multiple centers are needed to confirm findings	Strong
12	Shen et al. [32]	2020	Case series	Five critically ill patients with laboratory-confirmed COVID-19 and ARDS	China	Body temperature, sequential organ failure assessment P/F, viral load, serum antibody titer, blood biochemical index, ARDS, and ventilatory and ECMO supports before and after convalescent plasma transfusion	Test if convalescent plasma transfusion may be beneficial in treatment of critically ill COVID-19 patients with severe ARDS	ARDS resolved in four patients at 12 days after transfusion, and three patients were weaned from mechanical ventilation within 2 weeks of treatment. Treatment with: convalescent plasma, steroids, and antiviral (lopinavir/ritonavir; interferon alpha-1b; favipiravir, arbidol; darunavir)	All five patients improved in clinical status	Limited sample size and study design	Medium
13	Du et al. [33]	2020	Cross-sectional	85 fatal cases with COVID-19	China	Medical history, exposure history, comorbidities, symptoms, signs, laboratory findings, CT scans, and clinical management	Report clinical features of 85 fatal cases with COVID-19 in two hospitals in Wuhan	ARDS: 63	N/A	Only fatal cases of COVID-19 included	Medium
14	Chen et al. [34]	2020	Retrospective single-center	99 patients with COVID-19 pneumonia	China	Epidemiologic, demographic, clinical, and radiological features and laboratory data	Clarifying epidemiologicaland clinical characteristics of COVID-19 pneumonia	17 with ARDS	N/A	Low sample size One center	Medium

(continued)

Table 18.3 (continued)

No.	Author	Year	Design	Sample size	Country	Data type	Aim of the study	Main findings	Conclusion	Limitations	Quality score
15	Chen et al. [35]	2020	Retrospective case series	Cohort of 799 patients: 113 died and 161 recovered	China	Clinical characteristics and laboratory findings	Delineate clinical characteristics of patients with COVID-19 who died	ARDS: 113	N/A	N/A	Strong
16	Ferrey et al. [36]	2020	Case study	A 56-year-old male with ESRD and COVID-19	USA	Clinical characteristics and laboratory findings	Case analysis	CT showing new multifocal bilateral patchy GGOs with predominantly peripheral distribution. Chest X-ray sequence with interval increasing patchy opacities in both lungs consistent with evolving infectious process	N/A	N/A	Medium
17	Chung et al. [37]	2020	Retrospective case series	21 patients with symptoms and COVID-19	China	CT findings	Assessing imaging features COVID-19	Of 21 initial chest CT scans, three showed normal.	N/A	N/A	Medium
								Of 18 patients with GGOs, consolidation, or both, 12 had only GGOs, and no patient demonstrated consolidation without GGOs. Of the 21 patients, one had one affected lobe, two had two affected lobes, three had three affected lobes, four had four affected lobes, and eight had disease affecting all five lobes. 7/21 patients demonstrated GGOs and/or consolidative opacities with a rounded morphology, three demonstrated a predominantly linear abnormality, four had crazy-paving pattern, and seven patients (21%) had peripheral distribution of disease. No patients had cavitation in the lung, discrete pulmonary nodules, pleural effusion(s), lymphadenopathy, underlying pulmonary emphysema, or fibrosis			

18	Huang et al. [1]	2020	Cross-sectional	41 patients with COVID-19	China	Epidemiologic, clinical, laboratory, and radiological characteristics and treatment /outcome data	Reporting epidemiology, clinical, laboratory, and radiological characteristics and treatment / clinical outcomes of COVID-19 patients	ARDS: 12	N/A	Low sample size One center	Medium
19	Beloncle et al. [38]	2020	Case series	25 patients with SARS-Cov-2-associated ARDS	France	Gas exchanges, respiratory system compliance, and hemodynamics assessed at two levels of PEEP (15 cmH2O and 5 cmH2O) within 36 h (day 1) and from 4 to 6 days (day 5) after intubation	Describe characteristics of respiratory mechanics of COVID-19-associated ARDS and, in particular, whether lungs are recruitable with high levels of PEEP	Systematic recruitment-to-inflation ratio assessment may help to guide initial PEEP titration to limit harmful effects of unnecessary high PEEP in COVID-19 crisis	N/A	Low sample size One center	Medium
20	Zhang et al. [39]	2020	Cross-sectional	17 patients with COVID-19 infection	China	Multi-detector CT scans	Assessing CT images of 17 patients with COVID-19 infection	12 patients had GGOs, and five had consolidation and GGOs. Distribution of abnormalities was in subpleural lung regions in 12, bilateral in 14, and unilateral in three patients. Both upper and lower lobes involved in 15 patients, upper lobe only was involved in two patients. Follow-up HRCT scan performed in five patients showed that three had markedly decreased consolidation, fibrotic changes developed, and the other two patients showed mild progression with increased extent and density of opacities	N/A	Low sample size One center	Medium

(continued)

Table 18.3 (continued)

No.	Author	Year	Design	Sample size	Country	Data type	Aim of the study	Main findings	Conclusion	Limitations	Quality score
21	Wu et al. [40]	2020	Retrospective cross-sectional	80 patients diagnosed with COVID-19	China	Multi-detector CT scans	Investigate chest CT scan findings in patients with confirmed COVID-19, and evaluate relationship with clinical features	GGOs, 73/80 cases; consolidation, 50 cases; and interlobular septal thickening, 47 cases.	The common chest CT findings of COVID-19 are multiple GGOs, consolidation,	Small number of patients with proven SARS-CoV-2 infection. No measure of histopathology changes	Medium
								Most lesions were multiple with an average of 12 ± 6 lung segments involved. The most common involved lung segments were the following: dorsal segment of right lower lobe, 69; posterior basal segment of the right lower lob,e 68; lateral basal segment of the right lower lobe, 64; dorsal segment of the left lower lobe, 61; and posterior basal segment of the left lower lobe, 65 patients. Correlation analysis showed pulmonary inflammation index was significantly correlated with lymphocyte and monocyte counts, CRP, procalcitonin, days from illness onset, and body temperature ($p<0.05$).	and interlobular septal thickening in both lungs, which are mostly distributed under the pleura		
								CT features – GGO, 73; consolidation, 50; interlobular septal thickening, 47; crazy-paving pattern, 23; spider web sign, 20; subpleural line, 16; bronchial wall thickening, 9; lymph node enlargement, 3; pericardial effusion, 4; pleural effusion, 5 patients			

22	Wang et al. [41]	2020	Retrospective single-center case series	138 patients with COVID-19	China	Epidemiologic, demographic, clinical, laboratory, radiological, and treatment data	Describe epidemiology and clinical characteristics COVID-19-infected pneumonia	ARDS: 22	N/A	N/A	Medium
23	Zhou et al. [42]	2020	Retrospective, multicenter cohort	191 patients with COVID-19 of whom 137 were discharged and 54 died in hospital	China	Epidemiologic, demographic, clinical, laboratory, radiological, and treatment data	N/A	Consolidation 112, GGO 136,bilateral pulmonary infiltration 143, ARDS 59	N/A	N/A	Medium

ARDS acute respiratory distress syndrome, *N/A* not available, *HD* hospital day, *GGO* ground-glass opacity, *SARS* severe acute respiratory syndrome, *RT-PCR* reverse transcription polymerase chain reaction, *LDH* lactate dehydrogenase, *qPCR* quantitative polymerase chain reaction, *COVID-19* coronavirus disease 19, *CT scan* computed tomography scan, *USA* the United States of America, *RNA* ribonucleic acid, *RCT* randomized controlled trial, *MSCs* mesenchymal stem cells, *ICU* intensive care unit, *COPD* chronic obstructive pulmonary disease, *tPA* tissue plasminogen activator, *P/F ratio* PaO2/FiO2 ratio, *ECMO* extracorporeal membrane oxygenation, *PEEP* positive end expiratory pressure, *HRCT* high-resolution computed tomography, *CRP C-reactive protein*

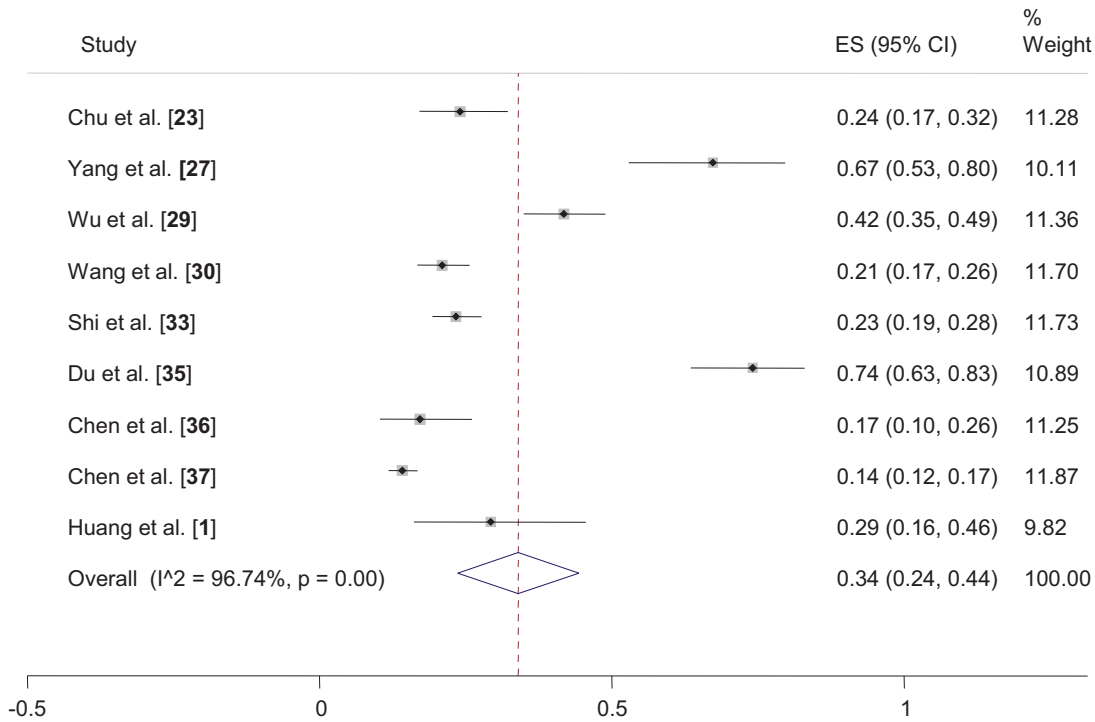

Fig. 18.4 The overall prevalence of COVID-19-induced ARDS determined from nine studies

full texts, while duplicate and unrelated articles were removed from the study. Lastly, 23 primary studies that met inclusion criteria were selected for appraisal and analysis [1, 21–42].

18.3.2 Study Descriptions

The study designs were diverse including cross-sectional, retrospective, case studies, or case series. All studies were published in the English language, most of them were conducted during the early phase of the COVID-19 pandemic in China [1, 24–35, 37, 39–42], two were carried out in the USA [23, 36], one was performed in Italy [22], one was in France [38], and one study was carried out during the SARS outbreak in China in 2003 [21]. The detailed characteristics of the 23 final primary articles are given in Table 18.3.

18.3.3 Methodological Quality Appraisal

The quality of all articles was evaluated using five-item mentioned tools, as shown in Table 18.3. Based on this scale, eight studies were ranked as having a strong quality, and 15 had a medium quality.

18.3.4 Narrative Summary and Brief of Themes

The data of the original articles were classified and discussed according to the following categories: (1) pathology of COVID-19, (2) diagnosis, (3) risk factors, (4) prevalence, and mortality, and (5) treatment.

18.3.4.1 Pathology of the COVID-19 Virus and ARDS

Biopsy samples taken from lung, liver, and heart tissue of a patient who died from COVID-19-related ARDS showed bilateral diffuse alveolar damage with cellular exudates, evident desquamation of pneumocytes, and hyaline membrane formation [26]. The left lung showed pulmonary edema with hyaline membrane formation. Both lungs showed interstitial mononuclear inflammatory infiltrates and multinucleated syncytial cells with atypical appearance in the intra-alveolar spaces. Blood analysis indicated an over-activation of T cells. An investigation using lung CT scans identified ground-glass opacities (GGOs) in 12 of 17 patients, and the remaining five patients showed a combination of GGOs and consolidation in the subpleural regions [39]. Follow-up scans performed on five patients showed development of fibrotic changes in three patients and mild progression with increased extent and density of GGOs in two patients. Another CT study of 80 COVID-19 patients found GGOs, consolidation, and interlobular thickening in the subpleural regions of both lungs in most cases [40]. Other studies showed that the medium time to development of ARDS from onset of symptoms in admitted patients ranged from 8 to 12 days [1, 41, 42].

Four studies of COVID-19 cases reported heterogeneous clinical manifestations, ranging from minimal symptoms such as fever, dry cough, or dyspnea to severe ARDS [23, 26, 30, 36]. Another study of two Chinese patients who developed symptoms while on holiday in Italy found GGOs with a crazy-paving pattern, slight unilateral pleural effusion, and mediastinal lymphadenopathies [22]. A study of an adult sickle cell patient with COVID-19 pneumonia using chest X-ray analysis found multifocal ill-defined opacities which worsened to GGOs and reticular opacities [23]. A retrospective case control study of patients with ARDS infected with either COVID-19 or H1N1 influenza found a higher frequency of coughing, fatigue, and gastrointestinal symptoms in the COVID-19 patients and higher sequential organ failure assessment scores in the H1N1 patients [30]. In addition, the COVID-19 patients had higher PaO_2/FiO_2 ratios, a higher proportion of GGOs, and lower mortality than the H1N1 patients. In addition, an end-stage renal disease patient in the USA who contracted COVID-19 disease while in hospital was found to have bilateral interstitial pneumonia, which worsened to ARDS [36].

18.3.4.2 Risk Factors

A one study of 133 patients with confirmed SARS (2003 outbreak of SARS-CoV) showed that advanced age, the presence of comorbidities, initial lactate dehydrogenase (LDH) levels, PCR test results of the nasopharyngeal specimen, and initial viral load were independently associated with ARDS [21]. Another study showed that advanced age and the presence of neutrophilia and organ and coagulation dysfunctions were contributing factors to development of ARDS and the progression from ARDS to death [27].

18.3.4.3 Diagnosis

Four studies showed that a decrease in the PaO_2/FiO_2 ratio, chest CT, and X-ray scan results could be used in the diagnosis of ARDS associated with COVID-19 infection [23, 26, 39, 40]. In addition, the severity of ARDS could be assessed as mild, medium, or severe using the PaO_2/FiO_2 ratio, as described earlier.

18.3.4.4 Prevalence and Mortality

The prevalence of COVID-19-related ARDS was reported by nine studies as follows: 32 out of 133 cases [21], 35 out of 52 critically ill cases [25], 84 out of 201 patients [27], 71 out of 339 cases [28], 97 out of 416 patients [31], 63 out of 85 cases) [33], 17 out of 99 patients [34], 113 out of 799 patients [35], and 12 out of 41 cases [1]. The overall prevalence of COVID-19-related ARDS was estimated as 34% using a random model (Fig. 18.4). The incidence of COVID-19-related ARDS in high-risk and critically ill patients was higher than for other cases [25, 33]. In addition, COVID-19-related ARDS resulted in a higher mortality rate. For example, the mortality rate was 60–61.5% in two studies of COVID-19 patients with ARDS **{Huang, 2020 #3}**[21, 25].

18.3.4.5 Treatment

Treatment and management of ARDS has been mostly supportive in nature. In the study by Chen et al. {Huang, 2020 #3}, transplantation of mesenchymal stem cells (MSCs) significantly lowered the mortality rate to 17.6% compared to 54.5% in the control group in patients with H7N9 influenza, demonstrating potential utility in COVID-19 ARDS cases [24]. In addition, this procedure had no adverse effects in the case of four patients who were followed over 5 years. A case series study by Wang et al. tested the effects of fibrinolytic therapy with tissue plasminogen activator in three COVID-19-related ARDS patients with transient improvements seen in all three cases [29]. Steroids such as methylprednisolone, antivirals (lopinavir, ritonavir, interferon alpha-1b, favipiravir, arbidol, darunavir), and antibacterial drugs have also been used for treatments, along with respiratory support [26, 27, 32]. However, the therapeutic benefits of these treatment strategies remain in question.

18.4 Discussion

Our findings indicate that approximately one-third of COVID-19 patients develop ARDS with common features of decreased PaO_2/FiO_2 ratios along with increased appearance of GGOs with consolidation by CT imaging. We found other risk factors for progression of COVID-19 patients to ARDS included advanced age, the presence of comorbidities, initial LDH levels, initial viral load, neutrophilia, as well as coagulation and organ dysfunction.

Increasing our understanding of the infection process of the SARS-CoV-2 virus is vital to improving patient outcomes during the current COVID-19 pandemic and future coronavirus and influenza outbreaks. It is now widely known that SARS-CoV-2 infection begins with entry of the virus via the upper airway followed by its migration down the respiratory tract to reach the gas exchange units of the lung. This leads to entry of the virus into the lung alveolar cells via ACE2 receptors. Once inside, the virus subverts the normal cellular processes enabling its replication and spreading to other organs and tissues of the body. During this process, an inflammatory response known as a "cytokine storm" can lead to pulmonary infiltration, cell death, and fibrosis, with development of ARDS [43].

The WHO interim guidelines recommend the use of extracorporeal membrane oxygenation (ECMO) to COVID-19 patients with ARDS [44]. Corticosteroids along with antiviral and antibacterial drugs have also been considered as potential treatments for ARDS because of their effects on reducing inflammation and fibrosis [3, 45]. However, none of these therapies are definitive cures for ARDS, and there have been some conflicting findings in this area. A recent trial in the UK found that the corticosteroid dexamethasone reduced mortality in COVID-19 patients receiving respiratory support [46], and early results from another trial conducted by Gilead showed that treatment with the antiviral drug remdesivir led to a nonsignificant reduction in the time to clinical improvement and duration of invasive mechanical ventilation compared to standard care [47]. However, further trials are required to confirm or refute the findings of both studies.

There are a number of limitations to the current study which makes definitive conclusions difficult. Most of these relate to the fact that we are still in the early phase of the COVID-19 pandemic, and a more complete picture is not likely to be available for several years to come. Therefore, we were only able to provide an estimate of the overall prevalence of ARDS in COVID-19 patients due to the low number of studies which have addressed this question thus far. For this reason, we also did not perform statistical methods of meta-analysis such as subgroup analysis or publication bias assessment and have only provided a summary of the results.

18.5 Conclusions

The current findings indicate that approximately one-third of patients with COVID-19 develop ARDS. Patients with ARDS are more likely to have a worse outcome and increased risk of death. For this reason, early detection of those patients

who are at increased risk of ARDS is critical. Further studies should be performed to identify biomarkers which indicate progression to ARDS such as the changes in the PaO_2/FiO_2 ratio and CT and X-ray imaging signs described here, as well as molecular biomarkers which can be sampled in body fluids. Likewise, further studies on the pathophysiology and distinct ARDS phenotypes should be conducted to enable identification of new treatment possibilities for improved patient outcomes.

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Competing Interests None declared.

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