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Post COVID-19 Organizing Pneumonia: A Systematic Review and Meta-analysis

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Authors' contributions

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

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ABSTRACT

Introduction: Several observational studies have found parallels between COVID-19 pneumonia and organizing pneumonia (OP). This study aims to investigate the published literature of OP related to COVID-19, estimates the prevalence of OP among COVID-19 patients, and assesses the risk or COVID-19 severity associated with OP.
Methodology: This was a systematic review and meta-analysis. A systematic electronic search through PubMed, Web of Science, Science Direct, EBSCO, and Google Scholar was conducted to include relevant and eligible literature. The authors used Review Manager 5.4 to perform quantitative data synthesis for the condition of interest analyses.
Results: A total of 9 eligible study articles and 12 case reports were included in this study. The estimated pooled organizing pneumonia prevalence among COVID-19 patients was 45.6% [23.1%-68.2%]. The association between OP and severe COVID-19 infection revealed a pooled OR [95% CI] of 5.22 [-0.96-11.41].

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Conclusion: COVID-19 patients had a rather high OP prevalence (43%). Surprisingly, cancer patients with COVID-19 infection had the lowest OP prevalence. OP was identified as a possible risk factor for the severity of COVID-19 infection.

Keywords: COVID-19, organizing pneumonia; secondary organizing pneumonia.

1. INTRODUCTION

By the end of 2019, a wave of pneumonia cases with unknown origins has emerged in Wuhan, China [1]. A few weeks later, in January 2020, deep sequencing analysis of lower respiratory tract samples identified a novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as the pathogenic agent for the observed pneumonia cluster. The World Health Organization (WHO) identified the SARS-CoV-2 epidemic as the new Coronavirus Disease 2019 on February 11, 2020. (COVID-19). The WHO declared the pandemic status on March 11, 2020, after 114 nations had been affected, with over 118,000 cases and over 4000 deaths [2].

Tyrell and Bynoe discovered and identified coronaviruses in 1966. Coronaviruses are enclosed, positive-sense, single-stranded RNA viruses that infect humans and many other animals [3]. At the time of writing (March 30, 2021), the COVID-19 pandemic had spread to 223 countries, with over 176 million confirmed cases and more than 3 million confirmed deaths estimated and recorded worldwide [4].

The most prevalent reason for hospitalization is viral pneumonia. More than 80% of patients are admitted to normal medical wards, with only a small proportion of intensive care units (ICU) [5]. According to a Chinese study, 16% of 1099 COVID-19 hospitalized patients had severe pneumonia, and 5% required ICU admission [6].

The presence of intra-alveolar buds of granulation tissue composed of fibroblasts and myofibroblasts combined with a loose connective matrix extending from the alveoli into the lumen of distal bronchioles is pathologically described as organizing pneumonia (OP). OP is an uncommon and distinct kind of interstitial lung disease (ILD) that is frequently attributed to idiopathic origins, a condition known as cryptogenic organizing pneumonia (COP). The "cryptogenic" nature of OP may be related to a lack of understanding of all entities, leading to secondary organizing pneumonia (secondary OP). A variety of known etiologies causes secondary OP, including infections (most usually viral-induced), medications, rheumatologic illnesses, aspiration, radiation, medications, and toxins [7-10].

Secondary OP has historically been linked to infections involving adenovirus, CMV, herpes virus, human immunodeficiency virus, parainfluenza virus, and influenza virus, possibly because to immune system stimulation by viral antigens. The link between COVID-19 pneumonia and the secondary OP has been brought into doubt, despite the fact that the evidence is restricted to a few case reports/series and post-mortem observations [11]. Based on current findings in the medical literature, this systematic review and meta-analysis aim to review the published literature of OP related to COVID-19 systematically and to analyze the prevalence of OP among COVID-19 patients and the risk of severity of COVID-19 associated with OP.

2. METHODOLOGY

2.1 Study Design and Duration

This systematic review and meta-analysis were conducted between March 15, 2021, and May 20, 2021.

2.2 Study Condition

This study investigates the published literature of OP related to COVID-19, estimates the prevalence of OP among COVID-19 patients, and assesses the risk or severity of COVID-19 associated with OP.

2.3 Search Strategy

An electronic systematic literature search of five major databases, PubMed, Web of Science, Science Direct, EBSCO, and Google Scholar, was conducted to include relevant and eligible literature. Our search process was limited to the English language and was specialized for each database as necessary. The relevant study articles were identified through the following keywords that adjusted into Mesh terms in

PubMed or subject terms as in Scopus; "Organizing pneumonia," "idiopathic bronchiolitis obliterans," "COVID-19", "Corona Virus Disease-2019", "2019-novel coronavirus", "severe acute respiratory syndrome coronavirus 2", and "(SARS-CoV-2)". The appropriate keywords were merged with Boolean operators such as "OR" and "AND." The search results were limited to full texts, freely accessible articles, human trials, and the English language.

2.4 Selection Criteria

Our review included the studies with the following criteria:

- Case reports of COVID-19 associated with OP.
- Study designs that provide the prevalence of OP among patients with COVID-19 or the risk of increasing COVID-19 infection due to OP.
- Adult patients are aging >18 years.

Exclusion criteria comprised the following:

- Studies with patients younger than 18 years.
- Studies not conducted in the English language.
- Studies with no free access.

2.5 Data Extraction

Rayyan (QCRI) [12] was utilized to determine the duplicate evaluation aspects of the search strategy outcomes. The researchers investigated titles and abstracts for convenience by screening the pooled search results using a set of inclusion/ exclusion criteria. The reviewers assessed the full text of the papers that met the inclusion criteria. The authors overcame any disagreements through debate and discussion. To include the eligible research, a data extraction form was created. The authors extracted information about the study titles, authors, study year, study design, study population, participant number, participant age (age range, mean age, or median age), and gender, the prevalence of OP, and the associated odds ratios representing the risk of COVID-19 infection severity associated with OP.

2.6 Risk of Bias Assessment

To evaluate the quality of the included studies, the Newcastle-Ottawa scale (NOS) [13] was utilized for qualitative and quantitative data synthesis for case-control, cohort, and cross-sectional studies. The Joanna Briggs Institute was used to assess the quality of the included case reports [14]. Any conflict in the quality evaluation was investigated and disputed by the reviewers. Visual inspection of the funnel plot was used to determine publication bias.

2.7 Strategy for Data Synthesis

Summary tables comprising the collected details from the eligible studies were presented to generate a qualitative overview of the included research features and outcome data. The extent of the recommended pooled analyses was examined once the data processing was assessed. Following the completion of data extraction in this meta-analysis, decisions were taken on how to better use case and control data and the numerical data of the included case reports. Independent of the viability of the pooled meta-analyses, a qualitative synthesis of the determined data was carried out. Studies that met the full-text inclusion requirements but did not provide numerical data on OP in COVID-19 patients.

The authors used Review Manager 5.4 (The Cochrane Collaboration) to perform quantitative data synthesis for the condition of interest analyses. The organizing pneumonia prevalence among COVID-19 patients as well as the risk of organizing pneumonia on the severity of the COVID-19 infection were evaluated using random-effects meta-analysis. As part of the pooled meta-analysis, heterogeneity was assessed using an I-square statistic. The funnel-plot and funnel-plot symmetry measurements were used to estimate publication bias. We used the Statistical Package for Social Sciences (SPSS version 26) to perform descriptive analyses conducted on cases extracted from case studies.

3. RESULTS

3.1 Search Results

The initial systematic search resulted in a total of 327 studies. Rayyan detected and removed 34 duplicate records from these studies (QCRI). Following the title and abstract screening, another 119 articles were deleted due to

irrelevant findings, incorrect research type or design, followed by the full-text assessment and removal of an additional 152 studies due to inappropriate analysis or improper outcome. This analysis eventually contained a total of 22 eligible study articles. The selection process and identification are presented in Fig. (1).

3.2 Characters of the Included Case Reports

Of the 12 included case reports, four cases were reported from Japan [15-18], two were reported from South Korea [19,20], one from Italy [21], one from Portugal [22], one from Saudi Arabia [23], one from China [24], and one from Austria [25]. Post-COVID-19 secondary OP was reported in all the case reports except Cappannoli *et al.,* who reported suspicion of amiodarone-induced OP, and Secondary bacterial OP reported by Al Zaki et al. (Table 1).

The youngest patient aging 27 years old male, was reported by Al Zaki *et al.* and was presented with a fever (38.5 C) with no other symptoms seven weeks; he had type 1 Diabetes Mellitus, aggravated by diabetes nephropathy with stage 4, secondary hyperparathyroidism, and high blood pressure. He also inherits the sickle cell trait and alpha thalassemia. While the oldest participant aged 84-year-old woman and presented with a 9-day history of physical aches and pains, she has a medical history of hypertension, hypercholesterolemia, and hypothyroidism [26].

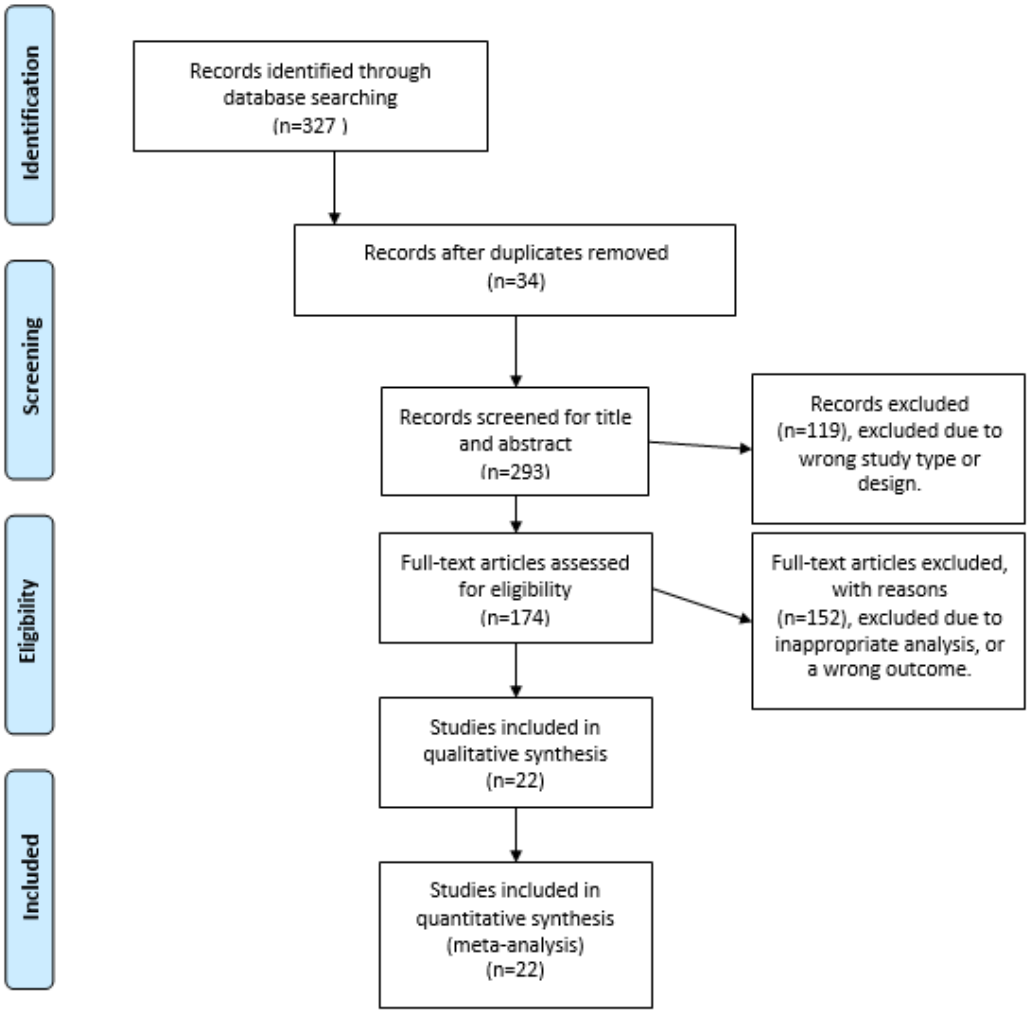

Fig. 1. PRISMA flowchart showing the selection process of eligible study articles

The highest temperature degree was found in a 71-year old male who presented with a seven-day fever (40°C) and a history of arterial hypertension and type 2 diabetes mellitus. He had been diagnosed with COVID-19 two days earlier when a nasopharyngeal swab was tested for RT-PCR. His CT scan revealed numerous bilateral ground-glass opacities in all pulmonary lobes, with a preference for peripheral and lower lobe distribution and no pleural effusions or adenopathies, indicating mild to severe COVID-19 pneumonia. On the 30th day of admission, a chest CT scan indicated patchy linear-band opacities with curvilinear morphology and peri-lobular distribution, which corresponded to the radiological pattern of OP, with >75 percent lung parenchymal involvement [22].

The lowest temperature degree was reported in a 46-year-old woman who presented with exertion-induced dyspnea, exacerbation of pneumonic infiltration, and hypoxia. Later, she was confirmed to have COVID-19. On room air, her body temperature was 36.5°C, her blood pressure was 140/90 mmHg, her pulse rate was 95 beats per minute, her respiratory rate was 22 breaths per minute, and her oxygen saturation was 88% [20].

Table 1. Summary of characteristics of the included case reports

Parameter	Study design	No. of cases	Country	Diagnosis
de Oliveira et al. 2021	Case report	3	Brazil	OP secondary to SARS-CoV-2 infection.
Simões et al. 2021	Case report	2	Portugal	Both of our patients' chest CTs revealed complete resolution of the OP pattern, with mild to moderate persistent pulmonary fibrosis and no honeycombing.
Seo et al. 2021	Case report	1	South Korea	This was a case of COVID-19-associated radiologically suspected OP with negative SARS-CoV-2 RT-PCR results from repeated NP swabs.
Al Zaki et al. 2021	Case report	1	Saudi Arabia	Secondary bacterial OP in a patient with COVID-19.
Funk et al. 2021	Case report	1	Austria	A patient with COVID-19 infection complicated with OP.
Bae et al. 2020	Case report	1	South Korea	A pathologically verified case with secondary OP developed following COVID-19 pneumonia recovery has been described.
Tamura et al. 2020	Case report	4	Japan	Secondary OP owing to severe COVID-19 infection.
Wu et al. 2020	Case report	1	China	A patient with COVID-19 infection presented with an OP pattern.
Cappannoli et al. 2020	Case report	1	Italy	A suspicion of amiodarone-induced OP was considered in the COVID-19 patient. The most common CT findings are septal thickening and interstitial pneumonia, both of which can lead to OP.
Okamori et al. 2020	Case report	2	Japan	The patients had pulmonary fibrosis abnormalities, including traction bronchiectasis and a significant reduction in lung volume. They were diagnosed with rapidly progressive OP.
Horii et al. 2020	Case report	1	Japan	This was a case with COVID-19-associated secondary OP characterized by repeated alterations in radiographic and laboratory results.
Kanaoka et al. 2019	Case report	2	Japan	Secondary OP among patients with COVID-19.

Table 2. Summary of characteristics of the included study articles

Study	Study design	Country	Total participants (COVID-19 Patients)	Condition	Prevalence (n)	Prevalence (%)	Odds ratio for COVID-19 severity, 95% CI
Jeong et al. 2021	Retrospective cohort study design	Korea	271	Organizing pneumonia	210	93	5.4 [-5.54, 16.29]
Cereser et al. 2021	Retrospective design	Italy	77	Organizing pneumonia	71	92	4.7 [-4.64, 14.01]
Kim et al. 2021	Retrospective design	Korea	123	Organizing pneumonia	54	43.9	
Cereser et al. 2021	Retrospective design	Italy	77	Organizing pneumonia	52	68	6.0 (-6.64, 18.64]
Elsoukkary et al. 2021		USA	32	Organizing pneumonia	8	25	
Carvalho et al. 2020	Retrospective design	Germany	157	Organizing pneumonia	77	49	
Werberich et al. 2020	Cohort study design	Brazil	48	Organizing pneumonia	7	14.6	
Borczuk et al. 2020	Multicenter retrospective study design	Italy and USA	68	Organizing pneumonia	23	33.8	
Rodríguez-Tajes et al. 2020	Prospective cohort design	Spain	61	Organizing pneumonia	16	26	
Ramtohul et al. 2020	Prospective design	France	70	Cryptogenic organizing pneumonia	8	11	

3.3 Characters of the Included Study Articles

Of the 10 included studies, two studies were conducted in Korea [27,28], two in Italy [29,30], one in Germany [31], one in Brazil [32], one in Spain [33], one in France [34], one in the United States (US) [35], and one in Italy and US [36]. The highest OP prevalence among COVID-19 patients was reported by Jeong et al., and the lowest prevalence was reported by Ramtohul et al. [34] (Table 2).

Regarding the sex, age, and laboratory findings in the included case reports, more than half of them (55%) were males, with mean age 62±14, and age ranges from 27-84 years. WBC count was reported in 4 patients only with mean record of 8750±6883 (/µL), creatinine level was reported in 8 patients 5.25±4.22 (mg/dL), creatine kinase was reported in only one patient 61 (U/L), D-dimer was reported in two patients 1.73±1.93 (µg/mL), PaO2/FiO2 (P/F) ratio was reported in 7 patients 131.7±42.2, temperature was reported in 11 patients 38.2±1º, heart rate was reported in 8 patients 97±13 (beats/ min), systolic blood pressure was reported in 9 patients 141±22 (mmHg), diastolic blood pressure was reported in 9 patients 83±9 (mmHg), respiratory rate was recorded in 3 patients 27±3 (mmHg), percutaneous oxygen saturation (SpO2) was reported in 9 patients 90±8%, diffusing capacity for carbon monoxide (DLCO) was reported in only one patient (83%), CPR was reported in two patients 252±49, macrophages were reported in two patients 0.9325±0.0035%, lymphocyte count was reported in four patients 11561±2494.43 (/µL), neutrophil count was reported in three patients 11561±2494.43 /µL, fibrinogen was reported in two patients 6.53±0.33 (g/L), LDH was reported in three patients 419±59 U/L, AST was reported in three patients 87±55 U/L, procalcitonin was reported in two patients 0.43±0.1 (ng/mL), ferritin was reported in five patients 785±594 (ng/mL), ALT was reported was reported in three patients 51±27 (U/L), and C-reactive protein (CRP) was reported in two patients 8.91±10.88 (mg/L). (Table 3).

Table 3. Sex, age, and laboratory findings of the patients included case reports

Parameter		n (%)/Mean±SD (Min-Max)	Missing data n (%)
Sex	Female	9 (45.0%)	0 (0%)
	Male	11 (55.0%)	
Age		62±14 (27-84)	0 (0%)
WBC count (/µL)		8750±6883 (3300-18200)	16 (80%)
Creatinine level (mg/dL)		5.25±4.22 (0.52-11.5)	12 (60%)
Creatine kinase (U/L)		61±. (61-61)	19 (95%)
D-dimer (µg/mL)		1.73±1.93 (0.36-3.09)	18 (90%)
P/F ratio		131.7±42.2 (61.6-170)	13 (65%)
P/F ratio after 10 days		230±. (230-230)	19 (95%)
Temperature (º)		38.2±1 (36.5-40)	9 (45%)
Heart rate (beats/ minute)		97±13 (78-120)	12 (60%)
Systolic blood pressure (mmHg)		141±22 (113-186)	11 (55%)
Diastolic blood pressure (mmHg)		83±9 (67-94)	11 (55%)
Respiratory rate (breaths/ minute)		27±3 (24-29)	17 (85%)
Percutaneous oxygen saturation (SpO2) (%)		90±8 (72-96)	11 (55%)
DLCO (%)		83±. (83-83)	19 (95%)
CPR		252±49 (217-287)	18 (90%)
Macrophages (%)		0.9325±0.0035 (0.93-0.935)	18 (90%)
Lymphocytes (/µL)		1315±1215.8 (510-3100)	16 (80%)
Neutrophils (/µL)		11561±2494.43 (8683-13100)	17 (85%)
Fibrinogen (g/L)		6.53±0.33 (6.3-6.76)	18 (90%)
LDH (U/L)		419±59 (351-454)	17 (85%)
AST (U/L)		87±55 (45-149)	17 (85%)
PCT (ng/mL)		0.43±0.1 (0±.36-0.5)	18 (90%)
Ferritin (ng/mL)		785±594 (269-1574)	15 (75%)
ALT (U/L)		51±27 (35-82)	17 (85%)
CRP (mg/L)		8.91±10.88 (1.22-16.6)	18 (90%)

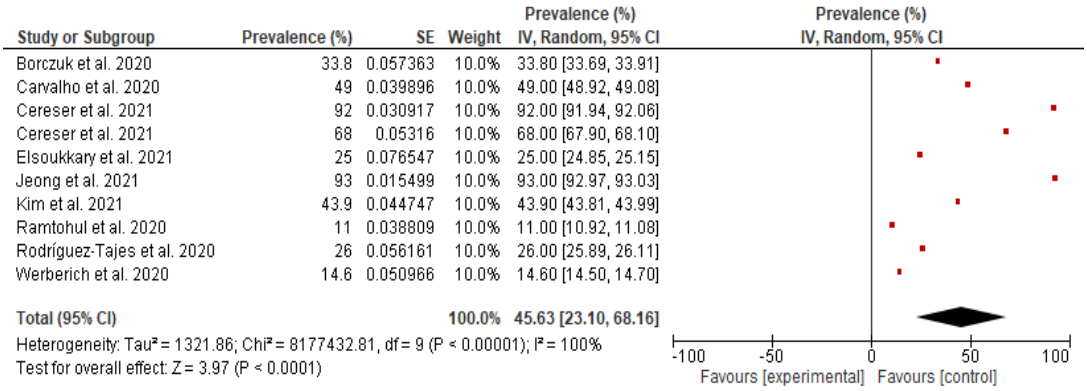

Fig. 2. Forest plot of the prevalence of organizing pneumonia among COVID-19 patients

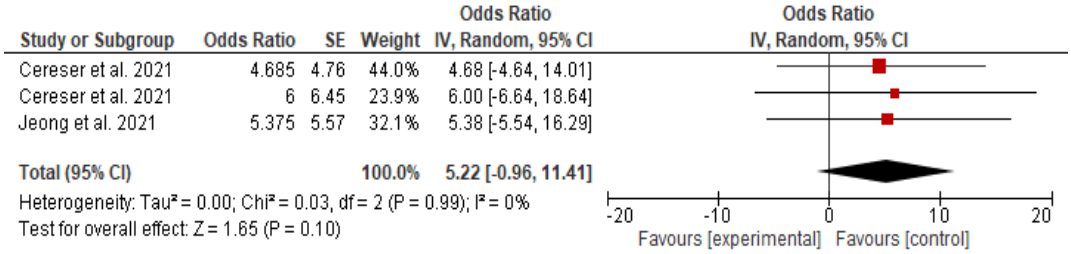

Fig. 3. Forest plot of the risk of COVID-19 severity due to organizing pneumonia

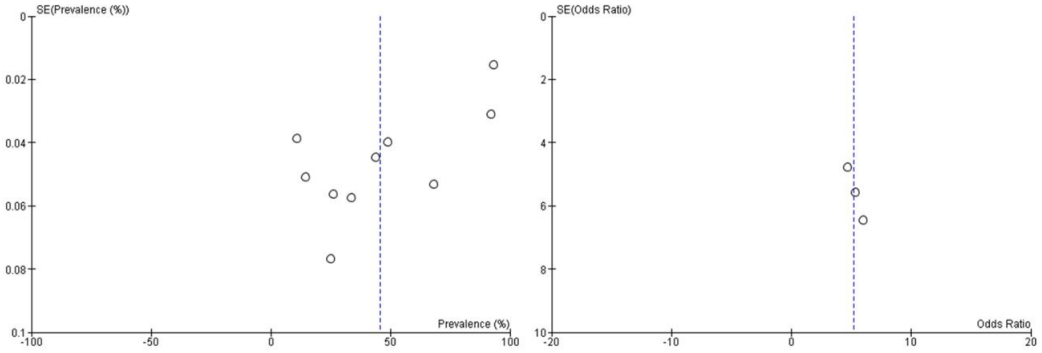

Fig. 4. Funnel plots to test publication bias of the included studies

3.4 Prevalence of Organizing Pneumonia among COVID-19 Patients

Using a random-effects model meta-analysis (Fig. 2), the estimated pooled OP prevalence among COVID-19 patients was 45.6% [23.1%-68.2%]. However, significant heterogeneity was observed (I^2=100%). Prevalence ranged from 11.0% [10.9%-11.1%], which was reported by [34], to as high as 93.0% [92.9%-93.0%], reported by [27].

3.5 Organizing Pneumonia as a Risk for Severe COVID-19 Infection

A random-effects meta-analysis (Fig. 3) was conducted to pool the odds ratios for the association between OP, and severe COVID-19

infection revealed a pooled OR [95% CI] of 5.22 [-0.96-11.41] with no significant heterogeneity detected (I^2=0%, P=0.99).

3.6 Publication Bias and Inter-study Heterogeneity

Visual inspection of the forest plots (Figs. 4a, 4b) reveals the asymmetrical distribution of the prevalence (Fig. 4a) and odds ratio (Fig. 4b) data of the included studies. Higgin's I^2 test revealed significant heterogeneity among the pooled prevalence data (I^2=100%); however, no significant heterogeneity was detected in the assessment of organizing pneumonia as a risk for severe COVID-19 infection by pooling odds ratios from 3 studies.

4. DISCUSSION

Moreover, numerous observational studies have evaluated the various phases of COVID-19 pneumonia from the time of disease onset [37-40]. This systematic review and meta-analysis investigating the clinical and laboratory finding reported in single case studies with OP among COVID-19 patients. Additionally, we estimate the prevalence of OP in patients with COBID-19 infection and the severity of this infection due to OP.

This study reported pooled prevalence of OP among COVID-19 patients 45.6% [23]. 1%-68.2%]. The highest OP prevalence was demonstrated among COVID-19 patients in Korea (93%) [27] and the lowest among cancer patients with COVID-19 infection (11%) [34]. The median duration from the beginning of infection to the start of dyspnea is 8 (5-13) days, but the duration to develop ARDS and ICU admission is 12 (8-15) days [41,42]. The mean age of diagnosis in OP is 59.0 +/- 13.6 years, with non-specific symptoms frequently characterized as a flu-like sickness [9,43]. Similar to COVID-19, OP symptoms are generally modest at first, with sub-acute manifestation over a few weeks [7,10]. Because of the mild and non-specific character of the presentation, the diagnosis of OP may take up to 2-3 months [9]. Fever and a shorter duration of symptoms are frequently useful indicators of an infectious etiology for secondary OP [7,44].

COVID-19-related ARDS does not appear and proceed in the normal ARDS pattern, with clinical symptoms frequently discordant with the severity of laboratory and radiologic findings [45]. 16 Furthermore, lung compliance may be normal to high, and the 8-12-day start of COVID-19-related ARDS is inconsistent with ARDS Berlin criteria, which define ARDS start within a week of a recognized injury [41,42,45].

In this study, we found that OP represents a potential risk factor in increasing the severity of COVID-19 infection OR=5.22 [-0.96-11.41]. In OP, coagulative protein leakage occurs after alveolar damage, causing a buildup of fibrin from decreased fibrinolytic activity, as well as fibroblast activation and proliferation, resulting in the development of intra-alveolar granulation tissue buds (Masson bodies) [11]. Acute fibrinous and OP (AFOP), sometimes known as a severe type of OP, is distinguished by significant intra-alveolar fibrin deposition known as "fibrin balls" as opposed to hyaline membranes found in diffuse alveolar damage (DAD) [43,46].

In up to 44% of instances, histological evidence of OP was seen in two large post-mortem lung exams of 100 patients diagnosed with COVID-19 [35,36]. The deceased's disease lasted a long period [median 20 (5-58) days]. Histopathological signs of AFOP were documented in autopsies of six patients with COVID-19 who died later in their illness course (20 days after the beginning of symptoms) [47].

Many single cases and case series were reported in the literature presenting and investigating the association between OP and COVID-19 infection. We retrieved and included twelve case reports in this study with 20 patients, 55% of them were males, and with a mean age of 62±14. Consistent with earlier COVID-19 findings, the presence of GGO was the dominating finding in the OP pattern, followed by mixed GGO and consolidation, with peripheral and lower lobe distribution [11]. In COVID-19, 74.5% of OP pattern instances were non-severe, resulting in moderate lung damage in the majority of OP instances. In terms of clinical outcome, the majority of OP pattern patients had a positive prognosis after discharge. This was similar to the prior OP research [9].

5. CONCLUSION

This systematic review and meta-analysis reported a relatively high OP prevalence among COVID-19 patients (43%). Interestingly, the lowest OP prevalence among cancer patients with COVID-19 infection. OP was represented as a potential risk factor for COVID-19 infection. We

hope that a large, well-designed study can be implemented to determine the relationship of OP secondary to COVID-19 infection as our knowledge grows during this current pandemic, with lung biopsies becoming increasingly warranted and performed in COVID-19 patients under the guidance of proper infection control protocol.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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