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RESEARCH ARTICLE

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Prevalence and clinical outcomes of pleural effusion in COVID-19 patients: A systematic review and meta-analysis

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Abstract

Observational studies indicate that pleural effusion has an association with risk and the clinical prognosis of COVID-19 disease; however, the available literature on this area is inconsistent. The objective of this systematic review and meta-analysis is to evaluate the correlation between COVID-19 disease and pleural effusion. A rigorous literature search was conducted using multiple databases. All eligible observational studies were included from around the globe. The pooled prevalence and associated 95% confidence interval (CI) were calculated using the random effect model. Mantel–Haenszel odds ratios were produced to report overall effect size using random effect models for severity and mortality outcomes. Funnel plots, Egger regression tests, and Begg–Mazumdar's rank correlation test were used to appraise publication bias. Data from 23 studies including 6234 COVID-19 patients was obtained. The overall prevalence of pleural effusion in COVID-19 patients was 9.55% (95% CI, $I^2 = 92\%$). Our findings also indicated that the presence of pleural effusions associated with increased risk of severity of disease(OR = 5.08, 95% CI 3.14–8.22, $I^2 = 77.4\%$) and mortality due to illness(OR = 4.53, 95% CI 2.16–9.49, $I^2 = 66\%$) compared with patients without pleural effusion. Sensitivity analyses illustrated a similar effect size while decreasing the heterogeneity. No significant publication bias was evident in the meta-analysis. The presence of pleural effusion can assist as a prognostic factor to evaluate the risk of worse outcomes in COVID-19 patients hence, it is recommended that hospitalized COVID-19 patients with pleural effusion should be managed on an early basis.

KEYWORDS

COVID-19, pleural effusion, SARS-CoV-2, X-ray computed tomography, viral, pleural disease

1 | INTRODUCTION

In December 2019, a new infectious pathogen known as severe acute respiratory syndrome (SARS-CoV-2) came into sight in China. It was linked with an unexplained cause of pneumonia. The disease was later coined coronavirus disease 2019 (COVID-19).[1] Till now, more than 150 million people have been infected by this virus leading to more than 3.15 million deaths.[2] The clinical presentation of COVID-19 varies significantly, fluctuating from minimum symptoms to critical respiratory failure, septic shock, subsequently to multiorgan failure.[3,4] The spectrum of clinical symptoms of COVID-19 illness comprises fever, dry cough, fatigue, sore throat, and dyspnea, and headache, vomiting, diarrhea, anosmia, and loss of taste.[5,6]

Chest imaging is critical for diagnosing and evaluating the seriousness and extent of the spread of COVID-19 pneumonia.[7] A large number of COVID-19 patients have distinct chest imaging characteristics, such as ground-glass opacities alone or in combination with consolidation, vascular enlargement, and traction bronchiectasis.[8] Pleural effusion associated with COVID-19 is less common in clinical settings. Yu et al.[9] reported the prevalence of pleural effusion in 12.9% of the total 1663 hospitalized patients. Similarly, another study reported pleural effusion in just 2.6% of hospitalized patients.[10] The precise prevalence of pleural effusion in COVID-19 patients remained unknown.

To date, however, there are still significant literature gaps existing between COVID-19 and pleural effusion. The aim of this systematic review and meta-analysis is to evaluate the correlation between COVID-19 disease and pleural effusion and draw more generalized inferences about the effect of pleural effusion on severity and mortality in COVID-19 patients compared with patients without pleural effusion.

2 | METHODS

The current systematic review and meta-analysis is conveyed and inscribed in conjunction with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[11]

2.1 | Search strategy

A rigorous literature search was conducted using PubMed and Embase till April 2021. The MedRxiv and SSNR preprint servers were

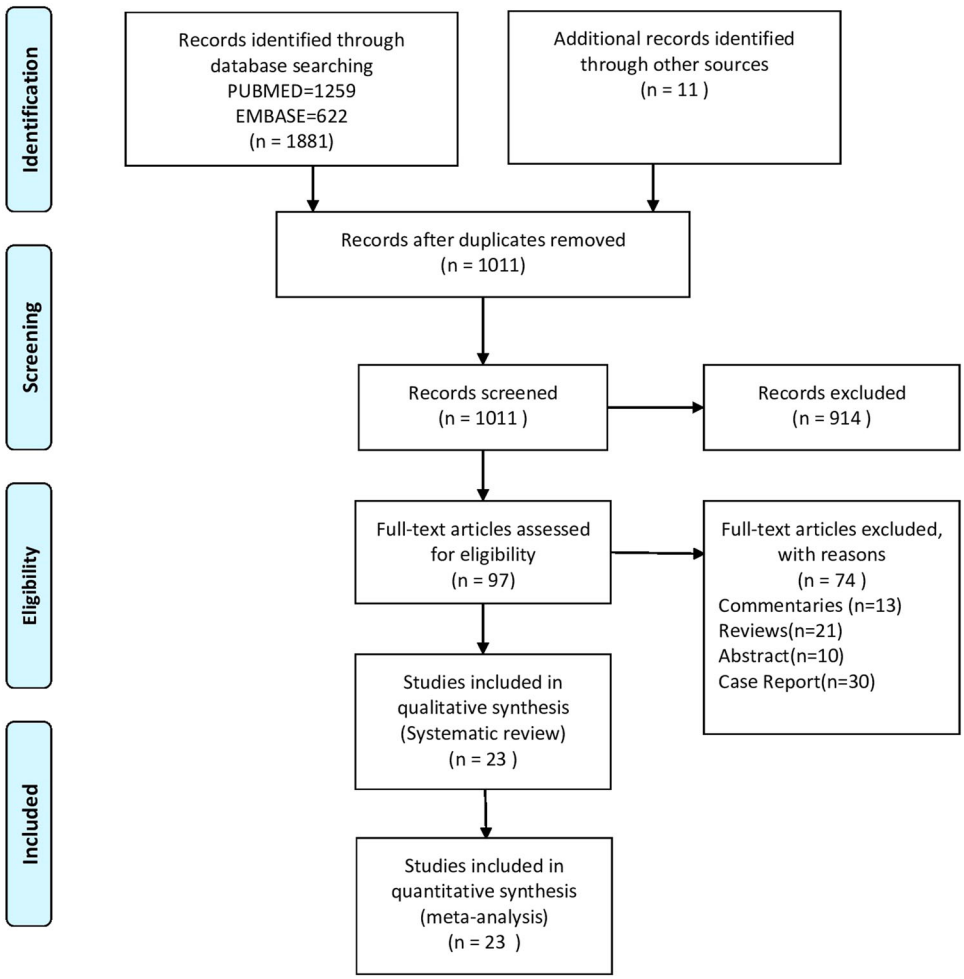

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

also screened. We united Medical Subject Headings (MeSH) terms and keyword and subsequent search terms, ([Coronavirus] or [COVID-19] or [SARS-CoV-2] AND [Pleural effusion] or [Chest imaging] or [Chest CT findings] or [Pleural disease]). Studies were included from all around the globe, with no language constraints. For more qualifying studies, we checked the reference lists of the incorporated studies and the relevant literature manually. Duplicate citations were eliminated and all residual articles were examined by their titles and abstracts to appraise eligibility. The PRISMA flow diagram is illustrated in Figure 1.

2.2 | Eligibility criteria

All eligible observational studies and case series were included for this meta-analysis. To be qualified for this meta-analysis, the article must satisfy the subsequent inclusion criteria: (a) Observational study or case series; (b) article describing pleural effusion and associated outcomes in COVID-19 patients; (c) studies with a sample size of ≥10 patients. These studies were incorporated irrespective of age, gender, ethnicity of the included patients.

The exclusion criteria were pre-determined as follows: (a) if no data regarding pleural effusion is given; (b) duplicate publications; (c) letters to the editor, case reports, commentaries, reviews, and posters. Following the implementation of these provisions, a thorough interpretation of the residual studies and data extraction were performed in an excel table.

2.3 | Study selection and quality assessment

Five authors separately reviewed the titles and abstracts of the earlier found articles. Based on the preset eligibility criterion, both authors distinguished studies separately. The conflict was resolved by negotiation and a previous understanding that another author (S.S.R.) would assess the unresolved dispute. The risk of bias assessment and quality appraisal of included studies was done with help of the Newcastle–Ottawa Scale (NOS).[12] Two of us (S.S.R.) and (C.R.T) independently employed the NOS for evaluating the individual quality of every study. The following sections were rated per study: low bias risk (8–9 points), moderate bias risk (5–7 points), and high bias risk (0–4 points).

2.4 | Data extraction

The data extraction for each study was autonomously progressed by five authors and was cross verified to depreciate errors. From each study, several details were retrieved including the First author name, the origin country of study, study design, total sample size, number of patients with pleural effusion, severe patients, the definition of severity, mortality, median age, gender (female sex proportion), respiratory disease proportion, diabetes proportion, and hypertension proportion as comorbidity.

2.5 | Statistical analysis

ReviewManager (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and MedCalc® Statistical Software version 19.6.4 (MedCalc Software Ltd.; https://www.medcalc.org; 2021) were used for all statistical analyses. The pooled prevalence and associated 95% confidence interval (CI) were calculated using the random effect model. Results for outcome analysis were presented as odds ratios (0Rs) with 95% confidence intervals (CIs) and pooled using the Mantel–Haenszel random-effects model. The I^2 statistics were used to assess the heterogeneity of effect size estimates across these studies with I^2 (low heterogeneity: $I^2 \leq 25\%$; moderate: 25%–50%; high >75%). Probability values less than 0.05 were considered statistically significant in all cases. A leave-one-out sensitivity analysis was also carried out to assess the effects of individual studies on the statistical results.

Publication bias was explored using funnel plots and Egger's regression test, and Begg–Mazumdar's rank correlation test.

2.6 | Grading quality of evidence

Quality of evidence for the primary and secondary outcomes was rated as high, moderate, low, and very low using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group approach.[13,14]

3 | RESULT

3.1 | Characteristics of the included studies

Precursory scans in multiple databases yielded 1892 articles. Of these, after eliminating duplicates, 1011 studies were evaluated. A total of 914 articles were additionally excluded after taking into consideration the title and abstract, generating 97 articles for adequate article review for conceivable consideration in this analysis. Eventually, 23 articles consisting of 6234 COVID-19 positive patients were included in this meta-analysis based on thorough evaluation and inclusion criteria.[9,10,15–35] The baseline characteristics of the included studies are outlined in Table 1. Of these included studies, many reports were from China ($n = 15$), followed by Iran with three studies and two studies from Italy. There was one study each from Brazil, the USA, and Egypt. The median age of included patients was 53.5 years with 40.8% of them being female. Among comorbidities considered, hypertension was present in 26.4% of patients and 14% of patients were having diabetes. Table 1 compiles the patient demographic and study characteristics.

TABLE 1 Patient demographic and study characteristics

Study	Country of origin	Study design	Sample size (*n*)	Mean age (years)	Female proportion (%)	Patients with PE	Definition of severe disease	Severe PE patients	Severe patients without PE	Respiratory disease proportion	Diabetes proportion	Hypertension proportion	NCOS (maximum score = 9)
Ashtari et al.[15]	Iran	Retro-spective	363	61.5	26	41	ICU admission + death	12	53	1.4	n/m	n/m	8
Barbosa et al.[16]	Brazil	Retro-spective	61	52	39.7	5	ICU admission	3	9	n/m	n/m	n/m	8
Chen Y et al. [17]	China	Retro-spective	37	58.7	43.2	3	RR > 30b/m, Spo2 < 93%, PaO2 ≤ 300 mmHg	1	21	19	24.3	45.9	7
Colombi et.[18]	Italy	Retro-spective	236	68	25	47	ICU Admission	28	80	17	16	n/m	8
Dai et al.[19]	China	Retro-spective	73	51	41	4	RR > 30b/m, Spo2 < 93%, PaO2 ≤ 300 mmHg	4	22	4	11	29	8
Emara et al.[20]	Egypt	Retro-spective	120	47.2	40.8	6	ICU admission	5	20	n/m	n/m	n/m	7
Feng et al.[21]	China	Retro-spective	442	53	43	25	MV + ICU + Shock	11	50	4.6	10.3	23.7	8
Ferguson et al.[22]	USA	Retro-spective	72	60.4	47.2	4	ICU admission	2	19	26.4	27.8	36.1	8
Huang et al.[23]	China	Retro-spective	103	57	41.7	3	n/m	1	35	n/m	n/m	n/m	7
Kazemi et al.[24]	Iran	Retro-spective	91	58	37.4	8	ICU admission + death	7	35	12.2	8.8	n/m	8
Li K et al.[25]	China	Retro-spective	83	45.5	47	7	MV + ICU + Spo2 < 93%	7	18	6	7.8	6	6
Liu k et al.[26]	China	Retro-spective	73		43.8	3	MV + ICU + Shock	3	0	n/m	n/m	n/m	7
Lyu et al.[27]	China	Retro-spective	51	54	43	10	MV + ICU	8	16	6	n/m	n/m	6
Peng et al.[10]	China	Retro-spective	651	46	46	17	ICU + Death	11	41	2	9	17	8
Salaffi et al.[28]	Italy	Retro-spective	165	61.5	20.6	12	MV + ICU + Spo2 < 93%	7	23	19	17.2	36	7

TABLE 1 (Continued)

Study	Country of origin	Study design	Sample size (*n*)	Mean age (years)	Female proportion (%)	Patients with PE	Definition of severe disease	Severe PE patients	Severe patients without PE	Respiratory disease proportion	Diabetes proportion	Hypertension proportion	NCOS (maximum score = 9)
Shi et al.[29]	China	Retro-spective	196	53	46.4	9	n/m	5	40	n/m	5.1	23.5	8
Tabatabei et al.[30]	Iran	Retro-spective	96	52.7	41.6	12	ICU admission	5	6	n/m	n/m	n/m	7
Wei et al.[31]	China	Retro-spective	827	51	45.5	76	Respiratory failure	34	112	3.26	12	22	7
Xu et al.[32]	China	Retro-spective	41	44	42	4	MV + ICU + Spo2 < 93%	2	11	n/m	n/m	n/m	6
Yu et al.[9]	China	Retro-spective	1663	64	49.6	216	RR ≥ 30b/m, Spo2 < 93%, PaO2 ≤ 300 mmHg	128	736	3.7	14.7	20.9	8
Yu et al.[33]	China	Retro-spective	70	49	40	15	MV + ICU + Spo2 < 93%	8	12	n/m	14.3	n/m	7
Zhan et al.[34]	China	Retro-spective	476	61.3	46.9	153	MV + ICU + Shock	66	29	4.8	14.7	29.6	8
Zhang et al.[35]	China	Retro-spective	244	55.3	40	12	n/m	n/m	n/m	2	16	28	8

Abbreviations: ICU, intensive care unit; MV, mechanical ventilation; n/m, not mentioned; NCOS, Newcastle–Ottawa Scale score; PaO2, partial pressure of oxygen; PE, pleural effusion; RR, respiratory rate; Spo2, oxygen saturation.

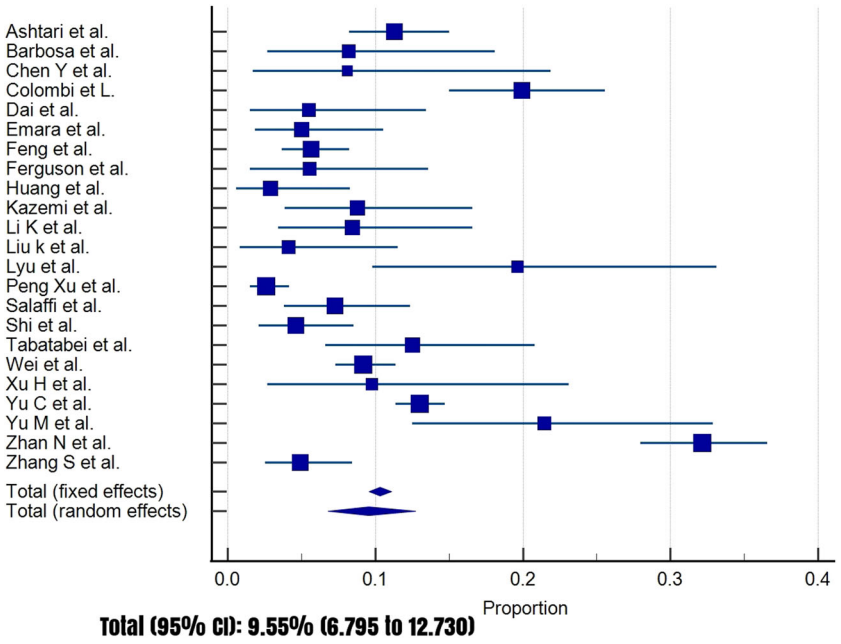

FIGURE 2 Forest plot for pleural effusion prevalence analysis

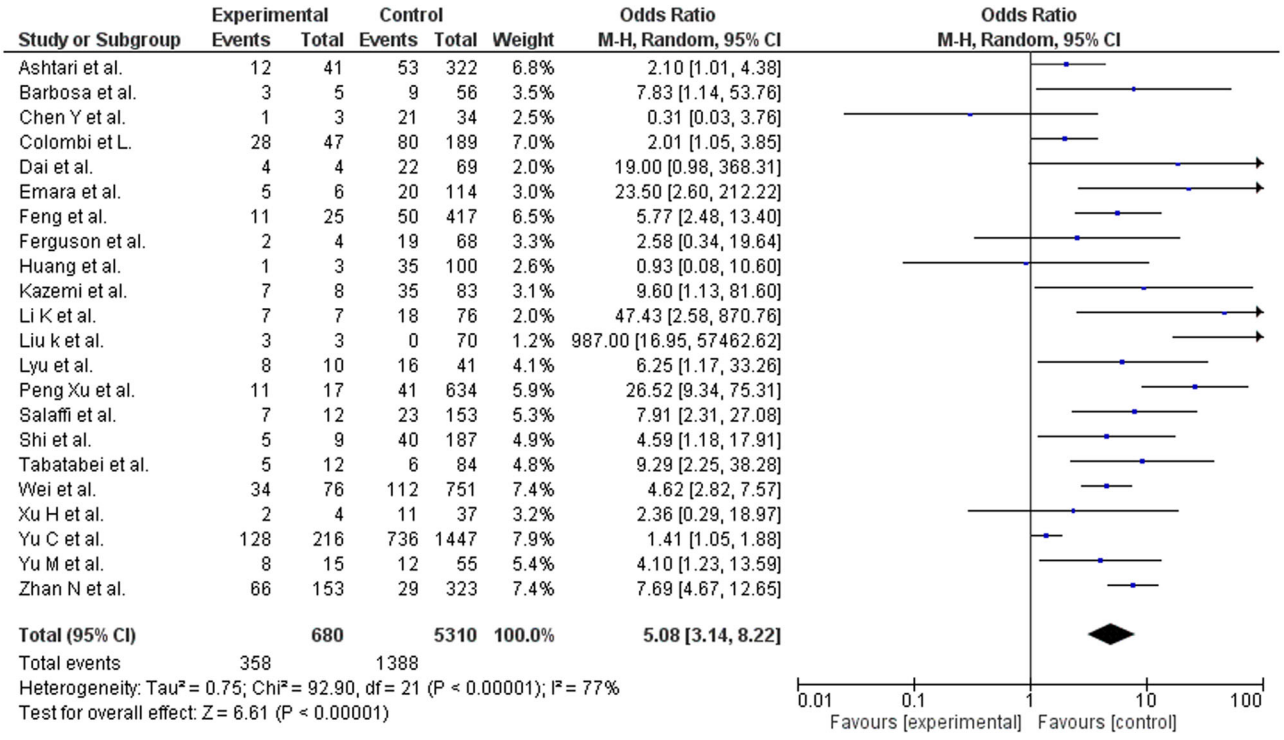

FIGURE 3 Forest plot for severity outcome analysis

3.2 | Meta-analysis for prevalence outcomes

Overall pooled random-effects estimate of pleural effusion in COVID-19 patients across studies was 9.55% (95% CI, 6.795–12.730). Test statistics results revealed high heterogeneity (I^2 =92%, $p < 0.0001$). This result was pooled from 23 studies that included 6234 patients (Figure 2).

3.3 | Meta-analysis for severity outcome

Meta-analysis findings revealed that the existence of pleural effusion in COVID-19 patients was associated with an increased risk of severity of disease compared to patients without pleural effusion.(OR = 5.08, 95% CI 3.14–8.22, $p < 0.0001$). Heterogeneity was high with I^2 = 77.4%. This result was pooled from 22 studies including

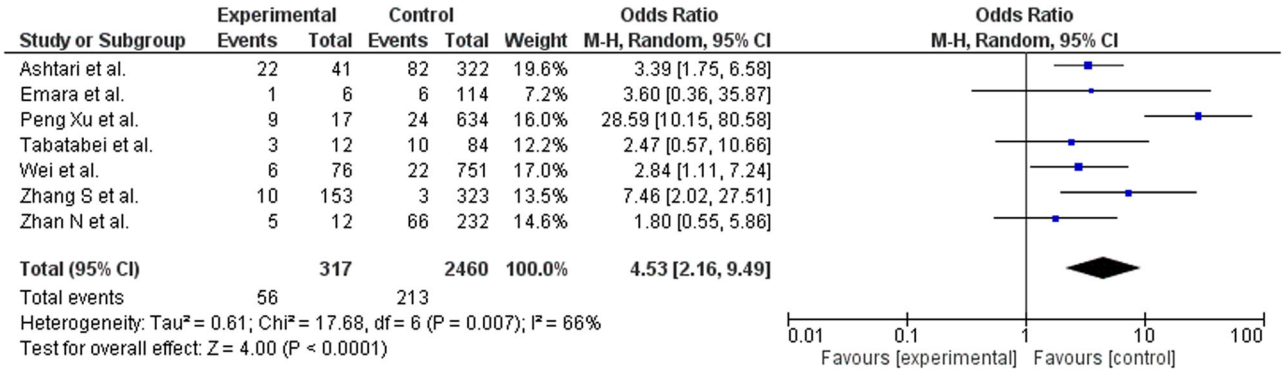

FIGURE 4 Forest plot for mortality outcome analysis

5990 COVID-19 patients (Figure 3). Due to the possibility of bias and imprecision, the certainty of the evidence was assessed as low by the GRADE system (Table S1).

3.4 | Meta-analysis for mortality outcome

Meta-analysis findings revealed that the existence of pleural effusion in COVID-19 patients was associated with increased odds of death from the disease compared to patients without pleural effusion. (OR = 4.53, 95% CI 2.16–9.49, $p < 0.0001$). Heterogeneity was moderate with $I^2 = 66\%$. This result was pooled from seven studies including 2777 COVID-19 patients (Figure 4). Due to the possibility of bias and imprecision, the certainty of the evidence was assessed as low by the GRADE system (Table S1).

3.5 | Sensitivity analysis

Sensitivity was calculated by systematically eliminating one study at a time to establish the results' robustness. Doing this did not lead to significant changes in the pooled OR estimate in both severity and mortality outcomes, consistent with the robustness of the result that pleural effusion in COVID-19 patients is associated with increased severity and mortality due to disease despite high heterogeneity. For severity outcome, exclusion of Yu C et al. leads to a significant decrease in heterogeneity from 77% to 56%, indicating that heterogeneity was most probably due to this study. Similarly, leaving out Peng et al. leads to a decrease in heterogeneity from 66% to 0 for mortality outcomes.

3.6 | Risk of bias assessment

The risk of bias assessment and quality appraisal of included studies was done with help of the NOS.[12] Out of 23 studies, 11 studies were of high quality, and 12 were of moderate quality with an average score of 7.34 (Table 1). Collectively, the evidence employed in these analyses was ascertained as being of high quality.

3.7 | Publication bias

Visual inspection of the standard funnel plots for the prevalence of Pleural effusion and both mortality and severity analysis were identified to be having substantial symmetry (Figure 5). Furthermore, evaluation of publication bias was also accompanied with the help of Egger's regression test and Begg–Mazumdar's rank correlation test. For both these tests, $p < 0.05$ was considered significant and analysis was deemed to be having publication bias. There was no apparent publication bias detected concerning prevalence analysis (Egger's test, $p = 0.581$; Begg–Mazumdar's rank correlation test, $p = 0.289$) and in mortality analysis (Egger's test, $p = 0.910$; Begg–Mazumdar's rank correlation test, $p = 0.652$). However, in severity analysis, egger's test showed a p-value < 0.05 ($p = 0.0170$) but Begg–Mazumdar's rank correlation test ($p = 0.297$), indicated no publication bias. Nevertheless, a leave-one-out sensitivity analysis indicated Yu et al.'s[9] study as the cause of publication bias, eliminating it leads to $p > 0.05$ in Egger's test ($p = 0.377$), signifying the role of this study in publication bias of severity analysis.

4 | DISCUSSION

The impact of the SARS-CoV-2 pandemic is catastrophic, as it has had healthcare, financial and social influence on millions around the world. Asymptomatic transmission, high infectivity, and droplet infection render management of this virus a horrible task. In the following systematic review and meta-analysis, we aimed to compile all available evidence by utilizing data of 6234 COVID-19 patients from 23 retrospective studies to determine the pooled prevalence of pleural effusion in COVID-19 and the effect of pleural effusion on the severity and mortality due to COVID-19 disease. The overall prevalence of pleural effusion in COVID-19 patients was found to be 9.55% (95% CI 6.79–12.73, $I^2 = 92\%$). Our result also illustrated that presence of pleural effusion in COVID-19 patients was associated with increased severity of disease(OR = 5.08, 95% CI 3.14–8.22, $I^2 = 77.4\%$) and mortality due to illness(OR = 4.53, 95% CI 2.16–9.49, $I^2 = 66\%$) compared with patients without pleural effusion. The results of our analysis suggest that pleural effusion could be an indicator of poor prognosis in COVID-19 patients.

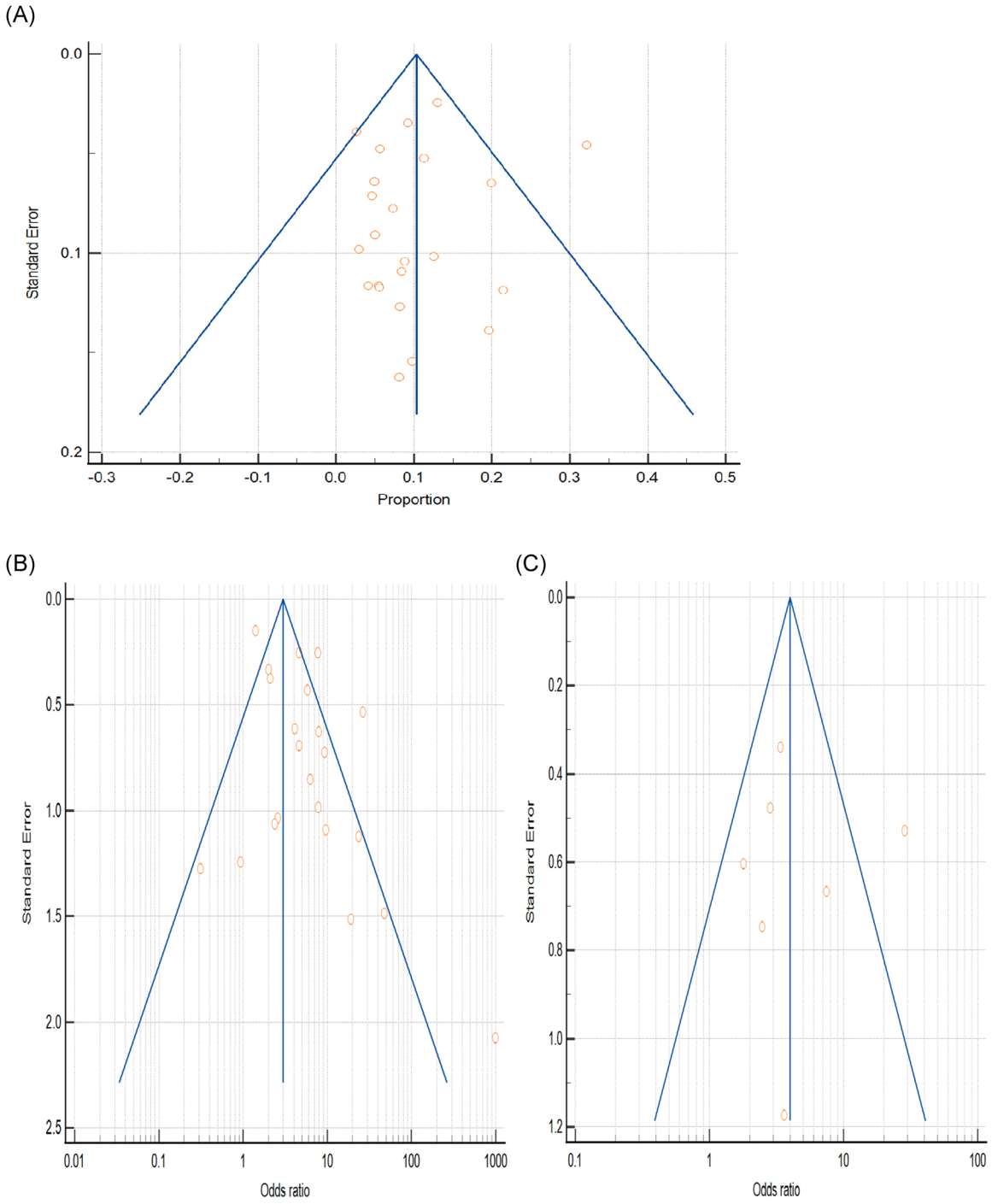

FIGURE 5 Funnel plots for publication bias. (A) Prevalence analysis; (B) Severity outcome; (C) Mortality outcome analysis

Despite the fact that the pathophysiology behind the lung injury in COVID-19 patients remains elusive, there are several proposed mechanisms. First is the binding of the SARS-CoV-2 virus through ACE2 receptors present in lung tissue leading to direct tissue injury.[36,37] SARS-CoV-2 invades the human cell via protein receptor angiotensin-converting enzyme 2 (ACE2) present in many organs of the human body including the lungs. This binding of the SARS-CoV-2 virus through ACE2 receptors present in lung tissue may be responsible for direct viral injury leading to lung inflammation. Systemic inflammatory response syndrome due to excess cytokine release arbitrated through pathologic T cells and monocytes is another proposed mechanism.[38,39] The more marked decreased lymphocytes, increased platelets, CRP, LDH, and D-dimer levels in COVID-19 patients with pleural effusion than patients without pleural effusion, suggest the role of sustained inflammatory response and cytokine storm as the pathological mechanism behind pleural effusion in COVID-19.[31,33]

The most conventional clinical symptoms of COVID-19 disease include fever, dry cough, fatigue, sore throat, and dyspnea, and headache.[40] In contrast to COVID-19 patients not having pleural effusion, the patients with pleural effusion often display more distinct symptoms like high fever, dyspnea, and aggravated cough.[34] Patients with and without pleural effusion often show significant variations in various laboratory parameters. Higher levels of white blood cells, neutrophils, C-reactive protein (CRP) ESR, and procalcitonin (PCT) in COVID-19 patients with pleural effusion indicate a severe infection in these individuals compared with patients without pleural effusion.[31] CRP and PCT level elevations are often predictive of a poor prognosis in COVID-19 patients.[41] Previous studies have reported that pleural effusion is an indicator of poor prognosis of the disease in adenovirus pneumonia, H5N1 viral pneumonia, and community-acquired pneumonia. Schoen et al.[42] reported that H5N1 patients with pleural effusion had a higher rate of worse outcomes (7%) than patients without pleural effusion (1%). Furthermore, bilateral pleural effusion was found to be linked with a seven-times surge in 30-day mortality in patients with community-acquired pneumonia.[43] Similarly, a study by Das et al.[44] on acute Middle East respiratory syndrome coronavirus infection (MERS-CoV), reported that patients with pleural effusion had higher short-term mortality indicative of poor prognosis. The authors reported that about 63.2% of those who died had developed pleural effusion than 13.9% ($p = 0.001$) of those who survived. Besides this, partial pressure of oxygen and oxygen saturation has been reported to be significantly lower in COVID-19 patients with pleural effusion than those without pleural effusion. This may be due to inhibition of respiratory function by pleural effusion, ultimately aggravating acute respiratory distress syndrome in these patients.[34] Patients with severe COVID-19 infection often advance quickly to acute respiratory failure, acute respiratory distress syndrome, metabolic acidosis, coagulopathy, and septic shock.[4] Thus, the presence of pleural effusion can assist as a prognostic factor to evaluate the risk of worse outcomes in COVID-19 patients. From a medical standpoint, based on existing evidence, it is recommended that hospitalized COVID-19 patients with pleural effusion should be managed on an early basis, owing to the risk of a worsening of the condition of patients.

There are several strengths of this article. This is the first systematic review and meta-analysis in our knowledge that illustrate the association between pleural effusion and odds of severe illness and mortality due to COVID-19. This systematic analysis of 23 indexed studies included from more than a year of publications from the start of the pandemic was performed to more reliably and accurately associate pleural effusion and COVID-19 illness-related outcomes. Another strength is that it incorporated the GRADE approach to rate the certainty of evidence. Nevertheless, there are some limitations of this meta-analysis that should be considered. Firstly, all the articles incorporated in the meta-analysis were retrospective studies in nature, and thus bias in data aggregation is an inherent concern. Secondly, We included few studies from preprint databases that did not go through peer review at that time. This was deemed a limitation, as peer reviewers could identify further inconsistencies in reporting methods and other details.

5 | CONCLUSION

Synopsizing the available evidence in the literature, the overall pooled prevalence of pleural effusion in COVID-19 patients was found to be 9.55%. Our findings, also indicate that the presence of pleural effusion in COVID-19 patients is associated with increased severity of disease and mortality due to illness compared with patients without pleural effusion. The presence of pleural effusion can assist as a prognostic factor to evaluate the risk of worse outcomes in COVID-19 patients hence, it is recommended that hospitalized COVID-19 patients with Pleural effusion should be managed on an early basis.

AUTHOR CONTRIBUTIONS

Conceptualization: Rathore Sawai Singh. *Data curation*: Rathore Shayan Saleemi, Gianpier Alonzo Rojas, Nabeel Hussain, Ade Harrison Manju, Sohaib Tousif, Camilo Andrés Avendaño-Capriles, Muhammad Adnan Ali, and Shayan Saleemi. *Formal analysis*: Rathore Sawai Singh, Qingqing Wen, Nabeel Hussain, and Maria Jose Hernandez-Woodbine. *Methodology*: Romil Singh, Priyanka Vatsavayi, Chenna Reddy Tera, Deep Manojkumar Patel, and Nabeel Hussain. *Writing—original draft*: Rathore Sawai Singh, Nabeel Hussain, and Ade Harrison Manju. *Writing—review and editing*: Rathore Sawai Singh, Qingqing Wen, and Romil Singh.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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