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Outcomes of atrial fibrillation in patients with COVID-19 pneumonia: A systematic review and meta-analysis

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ABSTRACT

Background: Recently, emerging evidence has suggested that atrial fibrillation (AF) has an epidemiological correlation with coronavirus disease 2019 (COVID-19). However, the clinical outcomes of AF in COVID-19 remain inconsistent and inconclusive. The aim of this study was to provide a comprehensive description of the impact of AF on the prognosis of patients with COVID-19 pneumonia.

Methods: Three electronic databases (PubMed, Embase, and Web of Science) were searched for eligible studies as of March 1, 2021. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the associations between AF (preexisting and new-onset) and in-hospital mortality, post-discharge mortality, and ventilator use.

Results: A total of 36 individual studies were incorporated into our meta-analysis. The combined results revealed that preexisting AF was associated with increased in-hospital mortality (pooled OR: 2.07; 95% CI: 1.60–2.67; $p < 0.001$), post-discharge mortality (pooled OR: 2.69; 95% CI: 1.24–5.83; $p < 0.05$), and ventilator utilization (pooled OR: 4.53; 95% CI: 1.33–15.38; $p < 0.05$) in patients with COVID-19. In addition, our data demonstrated that new-onset AF during severe acute respiratory syndrome coronavirus 2 infection was significantly correlated with increased mortality (pooled OR: 2.38; 95% CI: 2.04–2.77; $p < 0.001$).

Conclusions: The presence of AF is correlated with adverse outcomes in patients with COVID-19 pneumonia, which deserves increased attention and should be managed appropriately to prevent adverse outcomes.

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1. Introduction

Over the past year, coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has swept the globe with alarming morbidity and mortality [1]. While SARS-CoV-2 primarily infects the lungs, causing various pulmonary symptoms including cough and dyspnea with severe cases progressing to acute respiratory distress syndrome and death, it also affects multiple organs, particularly in the presence of complex cardiovascular comorbidities [2]. Published reports have detailed evidence that 20%–40% of hospitalized patients present with myocarditis, arrhythmias, acute coronary syndromes, fulminant heart failure, and cardiac death [3–6]. Acute respiratory tract infections are recognized triggers of acute exacerbations of cardiovascular diseases, while the underlying

cardiovascular diseases are often associated with comorbidities, which may result in elevated infection rates and mortality [2,7].

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide, sharing with COVID-19 a higher prevalence in populations with advanced age, cardiovascular risk factors, and comorbidities [8]. Approximately 20% of COVID-19 patients have been reported to have a history of AF, and new-onset AF represents a frequent complication, especially in those with severe cases [9]. Although there is emerging evidence suggesting an epidemiological association between AF and COVID-19, the understanding of clinical outcomes and prognosis of AF in COVID-19 is inconsistent and inconclusive. Some studies have indicated that AF, particularly new-onset, is an independent predictor of worse outcomes such as in-hospital mortality, mechanical ventilation, and cardiovascular death in patients with COVID-19 pneumonia [9–13], while others hold the view that the risk of mortality and mechanical ventilation are comparable with and without AF [14–16]. Given the ongoing controversial findings, it is necessary to perform a meta-analysis to systematically and comprehensively understand the impact of AF incidence on the outcomes of patients with COVID-19.

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The present study aimed to thoroughly summarize and evaluate the effects of AF (delineated as preexisting and new-onset) on clinical outcomes (in-hospital mortality, post-discharge mortality, and ventilator use) in patients with COVID-19.

2. Material and methods

2.1. Search strategy

This meta-analysis was performed following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [17] (Supplementary Material 1). We systematically searched three electronic databases (PubMed, Embase, and Web of Science) for potential studies that investigated the outcomes of AF in COVID-19 from inception to March 1, 2021. The primary search terms were “atrial fibrillation” and “COVID-19” or “severe acute respiratory syndrome coronavirus 2”. The search strategy for each electronic database was designed by an experienced medical librarian (Hai-bo, Zhou), and all steps of the search and study selection process were carried out by two independent investigators (Ming-yue Chen and Fang-ping Xiao). We also searched pertinent publications' reference lists for additional studies. Duplicate results were removed. No restrictions were placed on the type of study design included, but only studies published in English were eligible for inclusion in the meta-analysis.

2.2. Inclusion and exclusion criteria

A preliminary screening of titles and abstracts was carried out by two independent investigators, followed by a detailed reading of the full text to further assess if the articles met the inclusion criteria. Inclusion criteria consisted of the following: (i) observational studies enrolling patients with AF with a diagnosis of COVID-19; (ii) studies containing specific outcomes of interest (in-hospital mortality, post-discharge mortality, and ventilator use); and (iii) studies published in English. Studies were excluded if they contained the following: (i) review articles, case reports, communications, non-research letters, and commentaries; (ii) studies with samples <20; (iii) repeated population studies; and (iv) insufficient data to extract or estimate odds ratios (ORs) and 95% confidence intervals (CIs) of relevant outcomes of interest.

2.3. Data extraction and quality assessment

All candidate studies were independently evaluated by two researchers, and any discrepancies were resolved by a third reviewer (Lin Kuai). For each eligible study, the following data items were recorded: first author, publication year, setting, study design, total number of cases and gender, average study population age, and relevant outcome data (in-hospital mortality, post-discharge mortality, and ventilator use). Quality assessments were measured by two independent investigators using the Newcastle-Ottawa Scale (NOS) [18]. The NOS consists of three parts: selection (0–4 points), comparability (0–2

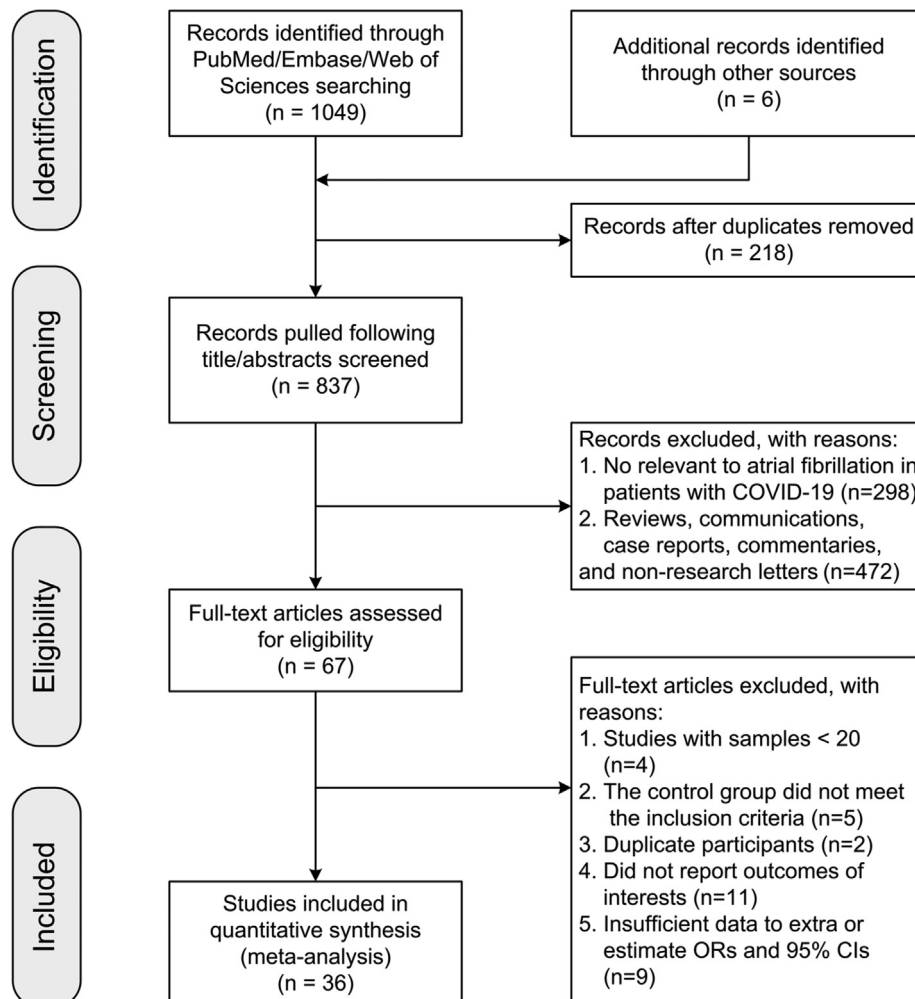


Fig. 1. Flowchart of study selection process. Abbreviations: COVID-19: coronavirus disease 2019; ORs: odds ratios; 95% CIs: 95% confidence intervals.

Table 1
Study characteristics and quality assessment

Study ID	Year	Setting	Study design	Patients with COVID-19 (M/F)	Age (median and range) (AF vs no AF)	ORs	NOS score (S C O)
Peltzer et al. [22]	2020	Multicenter, USA	Retrospective	1053 (653/400)	74.5 (± 13.0) vs 60.1 (± 17.0)	Adjusted	3 2 3
Rodilla et al. [23]	2020	Multicenter, Spain	Retrospective	12,226 (7018/5208)	67.5 ± 16.1 (overall)	Adjusted	3 2 1
Inciardi et al. [8]	2020	Single center, Italy	Retrospective	99 (80/19)	67 ± 12 (overall)	Unadjusted	3 0 3
Russo et al. [16]	2020	Multicenter, Italy	Retrospective	414 (253/161)	65.5 (± 15.5) vs 73.7 (± 9.9)	Unadjusted	3 1 3
Bhatla et al. [24]	2020	Single center, USA	Retrospective	700 (314/386)	N/A	Unadjusted	3 0 3
Yamada et al. [25]	2020	Multicenter, USA	Retrospective	210 (N/A)	N/A	Unadjusted	1 1 3
Atkins et al. [26]	2020	Multicenter, UK	Retrospective	507 (311/196)	74.3 ± 4.5 (overall)	Adjusted	2 2 3
Quisi et al. [27]	2020	Multicenter, Turkey	Retrospective	349 (153/196)	N/A	Unadjusted	3 1 3
Elias et al. [28]	2020	Multicenter, USA	Retrospective	1258 (685/573)	61.6 ± 18.4 (overall)	Adjusted	2 2 3
Wang et al. [29]	2020	Multicenter, China	Retrospective	319 (152/167)	64.97 ± 13.15 (overall)	Adjusted	3 2 2
Reilev et al. [30]	2020	Multicenter, Denmark	Retrospective	11,122 (4693/6429)	N/A	Unadjusted	3 1 1
Gerwen et al. [15]	2020	Single center, USA	Retrospective	3703 (2048/1655)	56.8 ± 18.2 (overall)	Adjusted	3 2 2
Peterson et al. [14]	2020	Single center, USA	Retrospective	355 (181/174)	66.21 ± 14.21 (overall)	Adjusted	2 2 3
Mccullough et al. [31]	2020	Single center, USA	Retrospective	754 (478/278)	63.3 ± 16.0 (overall)	Adjusted	3 2 2
Ghio et al. [32]	2020	Single center, Italy	Prospective	405 (278/127)	N/A	Unadjusted	2 1 3
Li et al. [33]	2020	Single center, China	Prospective	113 (68/45)	67.3 ± 14.1 (overall)	Unadjusted	3 1 1
Rodríguez-Molinero et al. [34]	2020	Multicenter, Spain	Retrospective	418 (238/180)	65.4 ± 16.6 (overall)	Adjusted	2 2 1
Clift et al. [35]	2020	Multicenter, UK	Prospective	6,083,102 (3,035,409/3047693)	N/A	Unadjusted	3 1 2
Shah et al. [36]	2020	Single center, USA	Retrospective	487 (N/A)	68.42 ± 16.70 (overall)	Unadjusted	3 1 1
Lano et al. [37]	2020	Multicenter, France	Retrospective	122 (79/43)	73.5 (64.2–81.2)	Unadjusted	3 1 1
Polverino et al. [38]	2020	Multicenter, Italy	Retrospective	3179 (2171/1008)	69.0 (57–78)	Unadjusted	3 1 1
Izurieta et al. [39]	2020	Multicenter, USA	Retrospective	25,333,329 (N/A)	N/A	Adjusted	2 2 1
Gue et al. [40]	2020	Single center, UK	Retrospective	316 (188/128)	N/A	Adjusted	3 2 2
Perez-Guzman et al. [41]	2020	Multicenter, UK	Retrospective	614 (382/232)	69 ± 25 (overall)	Adjusted	3 2 1
Canevelli et al. [42]	2020	Multicenter, Italy	Retrospective	415 (219/196)	84.3 ± 8.1 (overall)	Adjusted	2 2 3
Rossi et al. [43]	2020	Multicenter, Italy	Retrospective	590 (399/191)	76.2 (68.2–82.6, overall)	Unadjusted	3 0 2
Alvarez-Garcia et al. [44]	2020	Multicenter, USA	Retrospective	6439 (3547/2892)	63.5 ± 18 (overall)	Adjusted	2 2 2
Spinoni et al. [9]	2021	Multicenter, Italy	Retrospective	637 (N/A)	N/A	Adjusted	3 2 1
Özdemir et al. [12]	2021	Single center, Turkey	Retrospective	350 (194/156)	76 (64–82) vs 51 (37–65)	Unadjusted	4 1 2
Sanz et al. [13]	2021	Single center, Spain	Prospective	160 (96/64)	75.9 (± 9.6) vs 64.9 (± 16.3)	Unadjusted	4 1 1
Mountantonakis et al. [10]	2021	Multicenter, USA	Retrospective	2476 (1551/925)	73.1 (± 13.5) vs 73.6 (± 13.3)	Unadjusted	3 2 1
Poterucha et al. [45]	2021	Multicenter, USA	Retrospective	887 (N/A)	N/A	Unadjusted	3 0 1
García-Granj et al. [46]	2021	Single center, Spain	Retrospective	517 (290/227)	81.6 (± 8.7) vs 66.5 (± 14.9)	Unadjusted	3 1 1
Kelesoglu et al. [47]	2021	Single center, Turkey	Retrospective	658 (372/286)	54 ± 14 (overall)	Unadjusted	3 1 1
Denegri et al. [48]	2021	Single center, Italy	Retrospective	201 (N/A)	N/A	Adjusted	3 2 1
Zylla et al. [11]	2021	Multicenter, Germany	Retrospective	166 (108/58)	64.1 ± 16.7 (overall)	Unadjusted	3 1 1

COVID-19: coronavirus disease 2019; M/F: Male/Female; AF: atrial fibrillation; OR: odds ratio; NOS: Newcastle-Ottawa scale; S: selection; C: comparability; O: outcome; N/A: not available.

points), and outcome assessment (0–3 points). A study with a cumulative score of 6 or higher was considered high quality.

2.4. Statistical analysis

The pooled OR along with the corresponding 95% CI was calculated to analyze the correlation between AF and poor outcomes (in-hospital mortality, post-discharge mortality, and ventilator use) in patients with COVID-19 pneumonia. Adjusted ORs were directly utilized if they were reported in the candidate papers; otherwise, unadjusted ORs were estimated via crude data provided in the studies. An OR > 1 and 95% CI that did not contain the value 1 indicated a worse prognosis in COVID-19 patients with AF. The heterogeneity of the studies was determined using Cochran's Q test and the Higgins I-squared statistic, with a $P_h < 0.10$ or $I^2 > 50\%$ indicating significant heterogeneity [19]. A random-effects model was applied if substantial heterogeneity was observed and a fixed-effects model was adopted in all other cases. Subgroup analysis, sensitivity analysis, and meta-regression were used to investigate and clarify the heterogeneity among the studies. The possibility of publication bias was assessed by Begg and Egger tests, and p -values < 0.05 were considered statistically significant [20,21]. All statistical analyses were conducted using STATA version 16.0 (StataCorp, College Station, TX).

3. Results

3.1. Study characteristics

A total of 1055 papers were initially identified. After eliminating duplicates and carefully inspecting for inclusion and exclusion criteria,

36 studies published between 2020 and 2021 were included in our meta-analysis [8–16,22–48]. The flow diagram in Fig. 1 depicts the detailed study selection process. Of the 36 studies included, 12 were conducted in the United States [10,14,15,22,24,25,28,31,36,39,44,45], eight in Italy [8,9,16,32,38,42,43,48], four in Spain [13,23,34,46], four in the United Kingdom [26,35,40,41], three in Turkey [12,27,47], two in China [29,33], and one in Denmark [30], France [37], and Germany [11], respectively. Sixteen studies reported ORs and 95% CIs directly [9,14,15,22,23,26,28,29,31,34,39–42,44,48], while the ORs and 95% CIs of all others were estimated via the crude data provided in the article [8,10–13,16,24,25,27,30,32,33,35–38,43,45–47]. Fourteen of these were single-center studies [8,12–15,24,31–33,36,40,46–48], and 22 were multicenter studies [9–11,16,22,23,25–30,34,35,37–39,41–45]. Thirty-two studies were retrospective [8,9,12,14–16,22–31,34,36–44], and the remaining four studies were prospective [13,32,33,35]. In 23 studies, the NOS score was ≥ 6 [8–10,12–16,22–24,26–29,31,32,35,40–42,44,48], and in 13 the NOS score was < 6 [11,25,30,33,34,36–39,43,45–47]. The primary characteristics of the 36 studies are presented in Table 1.

3.2. Preexisting AF and in-hospital mortality

Twenty studies investigated the impact of preexisting AF on in-hospital mortality in COVID-19 patients [8,10–12,14,16,23,24,27,29,32–34,36–39,41,44,46]. Given the significant heterogeneity ($I^2 = 91.3\%$, $pH < 0.001$) among the included studies, a random-effects model was applied. Our results revealed that preexisting AF in patients with COVID-19 pneumonia was significantly correlated with increased in-hospital mortality, with a pooled OR of 2.07 (95% CI: 1.60–2.67;

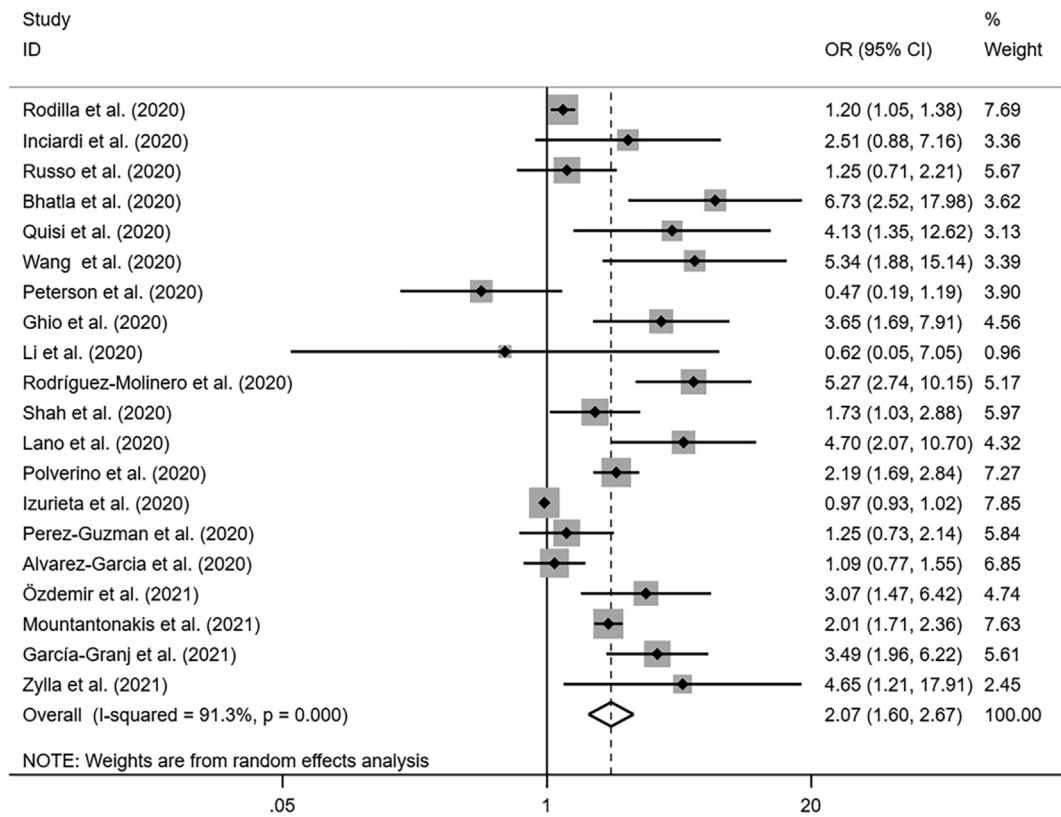


Fig. 2. Meta-analysis of the association between preexisting atrial fibrillation and in-hospital mortality in COVID-19 pneumonia. Results are presented as pooled ORs with 95% CIs. Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval.

$p < 0.001$; Fig. 2). In subgroup analysis by study setting, the pooled ORs for in-hospital mortality were 2.15 (95% CI: 1.17–2.67; $p < 0.05$) for single-center studies and 2.01 (95% CI: 1.51–2.68; $p < 0.001$) for multicenter studies. After stratification by sample size (< 200 and ≥ 200 participants), the combined ORs were 3.50 (95% CI: 1.98–6.17; $p < 0.01$) and 1.95 (95% CI: 1.50–2.54; $p < 0.0001$), respectively. Subgroup analysis based on extraction method found pooled ORs of 1.34 (95% CI: 1.01–1.78; $p < 0.05$) with the direct method and 2.49 (95% CI: 1.99–3.12; $p < 0.001$) with the indirect method. In addition, the combined ORs of NOS < 6 and NOS ≥ 6 were 2.47 (95% CI: 1.41–4.33; $p < 0.01$) and 1.85 (95% CI: 1.37–2.51; $p < 0.001$), respectively. Further information on the heterogeneity of each subgroup and the values calculated by the fixed-effects model are summarized in Table 2.

To further explore potential sources of heterogeneity, a sensitivity analysis was subsequently conducted. We excluded each eligible study sequentially to evaluate the influence of individual studies on the overall effect estimates. The result of sensitivity analysis suggested that no single study materially impacted the pooled summary

effect, which increased the credibility (Fig. 3). Additionally, meta-regression analysis showed that study setting ($p > |z| = 0.961$), cases ($p > |z| = 0.318$), and NOS scores ($p > |z| = 0.475$) did not significantly impact the heterogeneity of the pooled result, while the extraction methods ($p > |z| = 0.022$) may have significantly contributed to the heterogeneity. However, according to the results of subgroup analysis based on extraction method (i.e., for both direct and indirect extraction, the combined OR > 1 and 95% CI did not contain the value 1), we considered the result of our meta-analysis to be reliable and stable.

3.3. Preexisting AF and post-discharge mortality

Fourteen studies compared the post-discharge mortality of COVID-19 patients with and without preexisting AF [9,15,22,25,26,28,30,31,35,40,42,43,45,48]. The merged OR of post-discharge mortality was 2.69 (95% CI: 1.24–5.83; $p < 0.05$; Fig. 4), and this result showed significant heterogeneity ($I^2 = 98.5\%$, $pH < 0.001$). To explore sources of

Table 2
Subgroup analysis of in-hospital mortality

Analysis	N	R-OR (95% CI)	P	F-OR (95% CI)	P	I ²	Ph
In-hospital mortality	20	2.07 (1.60, 2.67)	0	1.10 (1.60, 2.67)	0	91.3%	0.000
Subgroup 1: Single center	7	2.15 (1.17, 2.67)	0.014	2.15 (1.58, 2.92)	0	70.2%	0.003
Multicenter	13	2.01 (1.51, 2.68)	0.000	1.09 (1.04, 1.13)	0	93.3%	0.000
Subgroup 2: Sample size <200	4	3.50 (1.98, 6.17)	0.003	3.50 (1.98, 6.17)	0	0.1%	0.391
Sample size ≥ 200	16	1.95 (1.50, 2.54)	0	1.10 (1.05, 1.14)	0	92.4%	0.000
Subgroup 3: Univariate analysis	13	2.49 (1.99, 3.12)	0	2.19 (1.95, 2.46)	0	46.9%	0.032
Multivariate analysis	7	1.34 (1.01, 1.78)	0.040	1.00 (0.96, 1.05)	0.888	87.1%	0.000
Subgroup 4: NOS <6	8	2.47 (1.41, 4.33)	0.002	1.02 (0.98, 1.07)	0.353	93.1%	0.000
NOS ≥ 6	12	1.85 (1.37, 2.51)	0	1.52 (1.38, 1.66)	0	81.7%	0.000

N: number of studies; R-OR: odds ratio calculated by random-effects model; F-OR: odds ratio calculated by fixed-effects model; 95% CI: 95% confidence interval; pH: P values of Q test for heterogeneity.

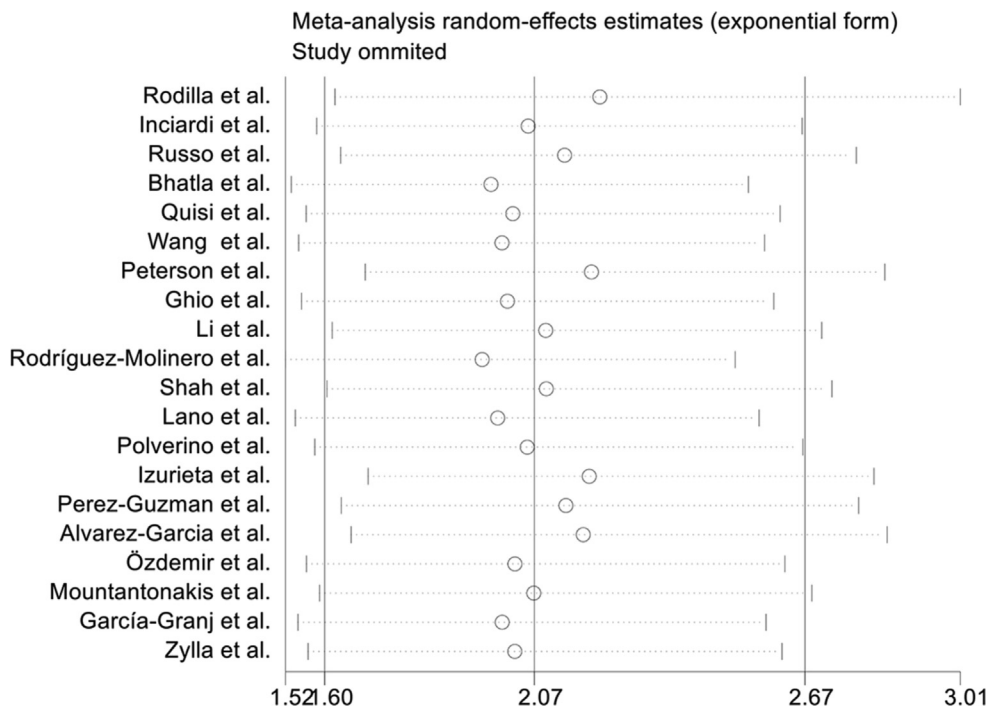


Fig. 3. Sensitivity analysis of the relationship between preexisting atrial fibrillation and in-hospital mortality in COVID-19 pneumonia.

heterogeneity, meta-regression was applied and the result demonstrated a significant effect of extraction method on the heterogeneity ($p > |z| = 0.005$), while the study setting ($p > |z| = 0.493$) and NOS scores ($p > |z| = 0.267$) were determined to be unimportant effect modifiers. After stratification by extraction method, the merged ORs were 1.60 (95% CI: 1.13–2.25; $p < 0.01$) with the direct method and 7.54 (95% CI: 3.18–17.88; $p < 0.001$) with the indirect method, suggesting the result was stable.

3.4. Preexisting AF and ventilator use

Six studies reported data on ventilator use associated with preexisting AF in COVID-19 patients [11,12,15,29,45,46]. The combined OR of ventilator use across these studies was 4.53 (95% CI: 1.33–15.38; $p < 0.05$; Fig. 5), with clear heterogeneity ($I^2 = 94.6\%$, $pH < 0.001$). Meta-regression analysis revealed that the extraction methods ($p > |z| = 0.744$), cases ($p > |z| = 0.342$), and NOS scores

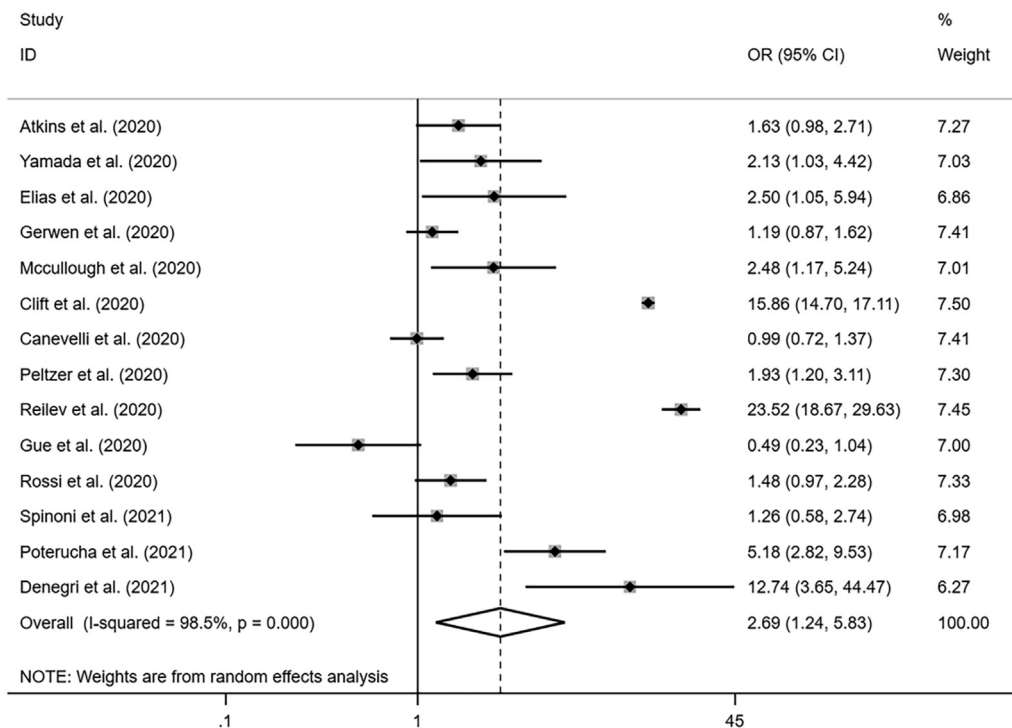


Fig. 4. Meta-analysis of the association between preexisting atrial fibrillation and post-discharge mortality in COVID-19 pneumonia. Results are presented as pooled ORs with 95% CIs. Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval.

($p > |z| = 0.319$) did not contribute to heterogeneity between the included studies, with only the study setting identified as a potential major source of heterogeneity ($p > |z| = 0.000$). Subgroup analysis based on study setting showed the pooled ORs for ventilator use were 1.52 (95% CI: 0.76–3.07; $p > 0.05$) for single-center and 14.48 (95% CI: 6.51–32.22; $p < 0.001$) for multicenter studies.

3.5. New-onset AF and mortality

Seven studies evaluated the impact of new-onset AF on mortality (including in-hospital and post-discharge mortality) in patients with COVID-19 pneumonia [9,10,13,16,22,45,47]. Owing to the fact that the heterogeneity among the studies was not significant ($I^2 = 42.0\%$, $pH = 0.111$), a fixed-effects model was applied for statistical analysis. The pooled results suggested a meaningful correlation between new-onset AF and increased mortality in patients with COVID-19 pneumonia (pooled OR: 2.38; 95% CI: 2.04–2.77; $p < 0.001$; Fig. 6).

3.6. Publication bias

Publication biases were assessed using Begg and Egger tests. For in-hospital mortality in patients with preexisting AF and COVID-19 pneumonia, we detected publication bias among the 20 included trials (Begg $Pr > |z| = 0.770$ and Egger $Pr > |t| = 0.000$). An Egger's publication bias plot is illustrated in Supplementary Fig. 1. The trim-and-fill method was performed to enroll missing studies, and the adjusted random-effects pooled OR of 1.794 (95% CIs: 1.411–2.280; Supplementary Fig. 2), was consistent with our primary analysis. For the meta-analysis of preexisting AF and post-discharge mortality in COVID-19 patients, although the Egger test indicated potential publication bias (Begg $Pr > |z| = 0.443$ and Egger $Pr > |t| = 0.003$), no study was imputed via the trim-and-fill method, and the adjusted random-effects pooled ORs remained 2.69 (95% CI: 1.24–5.83; $p < 0.05$). Furthermore, there was no evidence of publication bias for the analysis of preexisting AF and ventilator use (Begg $Pr > |z| = 0.707$ and Egger $Pr > |t| = 0.166$) or new-onset AF and mortality (Begg $Pr > |z| = 1.000$ and Egger $Pr > |t| = 0.744$).

4. Discussion

Since the beginning of the COVID-19 pandemic, a series of studies have reported data on the prognostic impact of AF on COVID-19 patients, though the results of these trials have remained inconsistent and inconclusive. Thus, we conducted this meta-analysis to synthesize all eligible studies into a more comprehensive understanding of the impact of AF (preexisting and new-onset) on the clinical outcomes of COVID-19 patients. The results of the current study revealed that preexisting AF is associated with increased in-hospital mortality (pooled OR: 2.07; 95% CI: 1.60–2.67; $p < 0.001$), post-discharge mortality (pooled OR: 2.69; 95% CI: 1.24–5.83; $p < 0.05$), and ventilator utilization (pooled OR: 4.53; 95% CI: 1.33–15.38; $p < 0.05$) in patients with COVID-19. In addition, our data demonstrated that new-onset AF in the context of COVID-19 pneumonia is correlated with increased mortality (pooled OR: 2.38; 95% CI: 2.04–2.77; $p < 0.001$).

The current meta-analysis incorporated four prospective studies and 32 retrospective studies, most of which reported poorer outcomes in COVID-19 patients presenting with AF than those without AF. A literature review published recently elaborated on the incidence, potential mechanisms, and clinical implications of AF in COVID-19 patients, suggesting that SARS-CoV-2 infection may increase susceptibility to AF and even worsen existing AF [49]. An earlier review summarized the possible mechanisms behind the association between AF and COVID-19 infection, detailing the contributions of myocardial microvascular pericytes, angiotensin, pulmonary hypertension, and regulatory T cells to COVID-19 [50]. Furthermore, Yang et al. performed a meta-analysis of studies published up to December 24, 2020, to explore the effect of AF on mortality in COVID-19, and the results supported a significant association between AF and increased mortality in patients with COVID-19 [51]. In 2021, a series of related papers have been published with clinical outcomes diversified beyond mortality. Our study incorporated these newly published studies and classified clinical outcomes into in-hospital mortality, post-discharge mortality, and ventilator use to explore their association with preexisting AF. Simultaneously, we reviewed studies that investigated new-onset AF during SARS-CoV-2 infection and demonstrated that new-onset AF was significantly associated with increased COVID-19 mortality, a finding that was not available in previous meta-analyses.

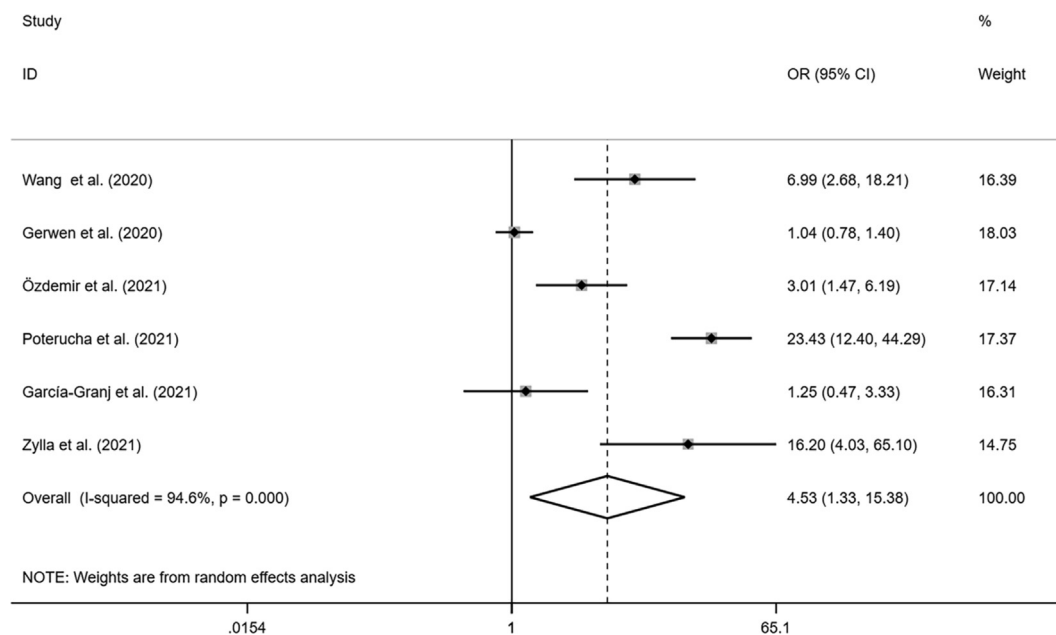


Fig. 5. Meta-analysis of the association between preexisting atrial fibrillation and ventilator use in COVID-19 pneumonia. Results are presented as pooled ORs with 95% CIs. Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval.

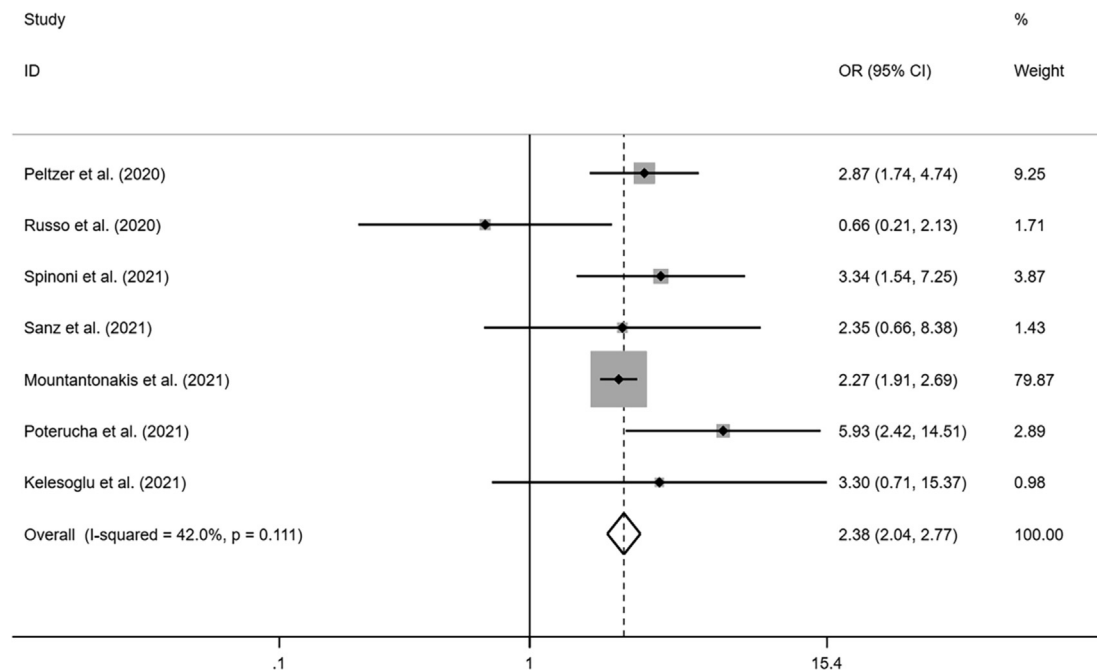


Fig. 6. Meta-analysis of the association between new-onset atrial fibrillation and mortality (including in-hospital and post-discharge mortality) in COVID-19 pneumonia. Results are presented as pooled ORs with 95% CIs. Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval.

As one of the most frequent cardiac arrhythmias, the prevalence of AF in the general population is approximately 0.4% to 1.0% [52], while in COVID-19 patients, the prevalence is even higher. A recent study conducted in northern Italy on 99 patients hospitalized with COVID-19 reported a prevalence of AF of 19%, increasing to 36% in patients with other cardiac diseases and 42% in deaths [8]. Another study performed in New York hospitals showed that of 1258 hospitalized COVID-19 patients, 14.3% were complicated by preexisting AF, and 10.1% with no history of AF experienced new-onset AF after admission. [53]. According to a small study by Fumagalli et al., an estimated 75% of geriatric patients present with a history of AF [54]. Furthermore, Wang et al. found that AF was present in 22% of critically ill patients who required mechanical ventilation [55]. AF shares with COVID-19 the risk factors of advanced age, cardiovascular conditions, and comorbidities. It has also been reported that during hospitalization with pneumonia, the increase of serum inflammatory cytokines and presence of acute metabolic disorders can trigger AF, particularly new-onset AF [13]. The inflammatory cytokine storm also contributes to COVID-19 patients' deterioration and accelerates the progression to severe pneumonia, multiple organ failure, or death. The connection between COVID-19-associated myocardial injury and AF may be manifested in any combination of contributors including systemic coagulation disorder, inflammation, stress cardiomyopathy, hypoxemia, and direct viral heart injury, which indicates that the impact the presence of AF has on COVID-19 patients goes beyond the category of simple arrhythmia [56]. Based on the current results, the presence of AF appears to act as a marker of elevated infection rates, and to some extent, to predict a worse prognosis. However, given that most of the studies we included were retrospective and there was a risk of residual confusion, further causality needs to be established by reliable prospective cohort studies.

Several limitations must be acknowledged in our meta-analysis. First, the quality of the reported data was relatively low, with most of the studies being retrospective in design, making them more vulnerable to bias. Second, there was significant heterogeneity in the combined results of preexisting AF and ventilator use. Although meta-regression revealed study setting to be the source of heterogeneity, the 95% CI of the pooled effect estimate of single-center contained the value 1,

which indicates that more prominent and reliable studies are needed to confirm their correlation. Third, subgroup analysis based on the extraction method found a pooled OR of 1.34 (95% CI: 1.01–1.78; $p < 0.05$) with multivariate analysis, indicating that the correlation between preexisting AF and in-hospital mortality was not very strong, for the number of enrolled studies was relative small, further studies are needed to confirm that AF is an independent risk factor. Fourth, too few published qualified studies to evaluate the correlation between new-onset AF and ventilator use, so we did not supply relevant parameters in the paper. Fifth, when the number of studies compiled in the meta-analyses is less than 10, the power of Begg and Egger tests is decreased substantially, which may lead to some undetected publication bias. Finally, only articles published in English were incorporated into our study, leaving the possibility that pertinent studies published in other languages were excluded.

5. Conclusion

Collectively, our study revealed that preexisting AF was associated with increased in-hospital mortality, post-discharge mortality, and ventilator use in COVID-19 patients, which suggests that preexisting AF predicts adverse prognosis to some extent. Moreover, we demonstrated that new-onset AF was significantly connected with increased mortality during SARS-CoV-2 infection. The current findings support a correlation between AF and adverse outcomes in patients with COVID-19 pneumonia; however, additional reliable studies are needed to further confirm that AF is an independent risk factor.

Availability of data and materials

Original data is available from the corresponding author on reasonable request.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajem.2021.09.050>.

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