A systematic review and meta-analysis of new-onset atrial fibrillation in the context of COVID-19

Sawai Singh Rathore[1], Akanksha Atulkar[2], Kavya Remala[3], Vanessa Vidaurre Corrales[4], Ameer Mustafa Farrukh[5], Ravinderjeet Kaur Puar[6], Sem Josue Nsanh Yao[7], Vijaya Durga Pradeep Ganipineni[8], Nirmal Patel[9], Naganath Thota[10], Ashish Kumar[11], and Abhishek Deshmukh[12]

[1]Dr Sampurnanand Medical College
[2]Global Remote Research Scholars Program
[3]Konaseema Institute of Medical Sciences and Research Foundation Hospital
[4]Universidad del Valle
[5]National University of Ireland Galway Academic Department of Paediatrics
[6]Vardhman Mahavir Medical College and Safdarjung Hospital
[7]Cincinnati Children's Hospital Medical Center Winslow
[8]Andhra Medical College
[9]St George's University School of Medicine
[10]Baptist Memorial Rehabilitation Hospital
[11]Cleveland Clinic Akron General Department of Internal Medicine
[12]Mayo Clinic Department of Cardiovascular Medicine

October 18, 2023

Abstract

Background: New-onset atrial fibrillation (NOAF) in COVID-19 raises significant clinical and public health issues. This systematic review and meta-analysis aims to compile and analyze the current literature on NOAF in COVID-19 and give a more comprehensive understanding of the prevalence and outcomes of NOAF in COVID-19. **Methods:** A comprehensive literature search was carried out using several databases. The random effect model using inverse variance method and DerSimonian and Laird estimator of Tua2 was used to calculate the pooled prevalence and associated 95% confidence interval (CI). Results for outcome analysis were presented as odds ratios (ORs) with 95% CI and pooled using the Mantel-Haenszel random-effects model. **Results:** The pooled prevalence of NOAF in COVID-19 was 7.8% (95% CI, 6.54% to 9.32%), pooled estimate from 30 articles (81,929 COVID-19 patients). Furthermore, our analysis reported that COVID-19 patients with NOAF had a higher risk of developing severe disease compared with COVID–19 patients without a history of atrial fibrillation (OR= 4.78, 95% CI 3.75 to 6.09) and COVID-19 patients with a history of pre-existing atrial fibrillation (OR= 2.75, 95% CI 2.10 to 3.59) . Similarly, our analysis also indicated that COVID–19 patients with NOAF had a higher risk of all-cause mortality compared with, COVID–19 patients without a history of atrial fibrillation (OOR= 3.83, 95% CI 2.99 to 4.92) and COVID-19 patients with a history of pre-existing atrial fibrillation (OR= 2.32, 95% CI 1.35 to 3.96). The meta-analysis did not reveal any significant publication bias. **Conclusion:** The results of the current meta-analysis a high prevalence rate of NOAF among COVID-19 patients. Further the study reported higher disease severity with NOAF compared with COVID-19 patients without a history of atrial fibrillation and with a history of atrial fibrillation.

A systematic review and meta-analysis of new-onset atrial fibrillation in the context of COVID-19

Running head: *NOAF in COVID-19*

Sawai Singh Rathore[1], Akanksha Atulkar[2], Kavya Remala[3], Vanessa Vidaurre Corrales[4], Ameer Mustafa Farrukh[5], Ravinderjeet Kaur Puar[6], Sem Josue Nsanh Yao[7], Vijaya Durga Pradeep Ganipineni[8], Nirmal Patel[9], Naganath Thota[10], Ashish Kumar [11,] Abhishek Deshmukh, [12]

[1] Department of Internal Medicine, Dr. Sampurnanand Medical College, Jodhpur, Rajasthan, India; [2] Global Remote Research Scholars Program, St. Paul, Minnesota, USA;[3] Department of Internal Medicine, Konaseema Institute of Medical Sciences, Amalapuram, India; [4] Department of Internal Medicine, Universidad Privada del Valle,Cochabamba, Bolivia;[5] Department of Internal Medicine, University of Galway School of Medicine, Galway, Ireland; [6]Department of Internal Medicine, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India; [7] Department of Internal Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [8] Department of Internal Medicine, Andhra Medical College, Visakhapatnam, India;[9] Department of Internal Medicine, St. George's University School of Medicine, Grenada; [10] Department of Internal Medicine, Baptist Memorial Hospital, Memphis, Tennessee, USA; [11]Department of Internal Medicine, Cleveland Clinic Akron General, Akron, OH, USA; [12] Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA.

Total Word Count: 2015 (Excluding title page, abstract, abbreviations, references, and figure legends)

Funding: None

Disclosure: None

Corresponding Author:

Abhishek J Deshmukh MBBS

Department of Cardiovascular Diseases

Mayo Clinic,

200 1st Street SW

Rochester, MN 55905

Deshmukh.abhishek@mayo.edu

ABSTRACT

Background: New-onset atrial fibrillation (NOAF) in COVID-19 raises significant clinical and public health issues. This systematic review and meta-analysis aims to compile and analyze the current literature on NOAF in COVID-19 and give a more comprehensive understanding of the prevalence and outcomes of NOAF in COVID-19.

Methods: A comprehensive literature search was carried out using several databases. The random effect model using inverse variance method and DerSimonian and Laird estimator of Tua2 was used to calculate the pooled prevalence and associated 95% confidence interval (CI). Results for outcome analysis were presented as odds ratios (ORs) with 95% CI and pooled using the Mantel-Haenszel random-effects model.

Results: The pooled prevalence of NOAF in COVID-19 was 7.8% (95% CI, 6.54% to 9.32%), pooled estimate from 30 articles (81,929 COVID-19 patients). Furthermore, our analysis reported that COVID-19 patients with NOAF had a higher risk of developing severe disease compared with COVID–19 patients without a history of atrial fibrillation (OR= 4.78, 95% CI 3.75 to 6.09) and COVID-19 patients with a history of pre-existing atrial fibrillation (OR= 2.75, 95% CI 2.10 to 3.59) . Similarly, our analysis also indicated that COVID–19 patients with NOAF had a higher risk of all-cause mortality compared with, COVID–19 patients without a history of atrial fibrillation (OOR= 3.83, 95% CI 2.99 to 4.92) and COVID-19 patients with a history of pre-existing atrial fibrillation (OR= 2.32, 95% CI 1.35 to 3.96). The meta-analysis did not reveal any significant publication bias.

Conclusion: The results of the current meta-analysis a high prevalence rate of NOAF among COVID-19 patients. Further the study reported higher disease severity with NOAF compared with COVID-19 patients without a history of atrial fibrillation and with a history of atrial fibrillation.

KEYWORDS : New-onset atrial fibrillation; COVID-19; SARS-CoV-2; atrial arrhythmias; heart rhythm; mortality

ABBREVIATIONS

COVID-19- Coronavirus disease- 2019

SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2

NOAF- New-onset atrial fibrillation

1. INTRODUCTION

SARS-CoV-2 causing COVID-19 has affected millions worldwide till date. Although initially described for its respiratory symptoms and complications, new research has highlighted the virus's wide-ranging effects, which go well beyond the respiratory system. The cardiovascular system has drawn much attention because of the various cardiac manifestations, calling for more research and comprehension

The development of new-onset atrial fibrillation (NOAF) in COVID-19 is one such cardiac manifestation. Several underlying cardiovascular and systemic conditions have been linked to atrial fibrillation. However, the intriguing link between COVID-19 and AF has created a particular focus in cardiovascular medicine, providing additional information about the underlying mechanisms, clinical implications, and potential therapeutic options. Although there are variations in the prevalence of NOAF in COVID-19 as documented by prior studies, it is clear that it can affect how the disease manifests clinically.'

The presence of NOAF in COVID-19 raises significant clinical and public health issues, related to the effect of NOAF in COVID-19 outcomes, such as mortality, hospitalization rates, and the course of the disease. Hence, we present a systematic review and meta-analysis to compile and analyze the current literature on NOAF in COVID-19. By combining data from various studies, we aim to provide a more comprehensive understanding of the prevalence, clinical importance, and potential underlying mechanisms of NOAF in COVID-19.

2. METHODS

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines are followed in communicating and processing the current systematic review and meta-analysis.

2.1 Search strategy:

A comprehensive literature search was conducted with PubMed and Embase until September 5, 2023. The MedRxiv and SSNR preprint servers were also filtered. We combined Medical Subject Headings (MeSH) terms and keywords, and subsequent search terms were, *(([Coronavirus] or [Covid-19] or [SARS-CoV-2] AND [New-onset atrial fibrillation] or [Atrial Fibrillation] or [Arrythmias] or [Outcomes]))* . There were no language or geographic restrictions. We manually searched the reference lists of the included studies and the relevant literature for additional qualifying studies. After removing duplicate citations, the eligibility of the remaining articles was evaluated by looking at their titles and abstracts. The PRISMA flow diagram is depicted in Figure 1.

2.2 Eligibility Criteria

All qualified studies were included in this meta-analysis. To be included in the present meta-analysis, the article must have full filled the following inclusion criteria: (a) an observational article reporting COVID-19 and prevalence of NOAF; (b) studies with a sample size of [?] 5 patients. These studies were included irrespective of the patient's age, gender, or ethnicity.

The following were the exclusion requirements: (a) lacking data on the outcome of COVID-19, (b) duplicate publications, (c) letters to the editor, case reports, commentaries, reviews, and posters.

2.3 Study selection and quality assessment:

Two authors () individually reviewed the titles and abstracts of the literature extracted from database search. Each author filtered the studies based on the predetermined eligibility criteria. Any conflict was resolved through discussion and an earlier agreement that a third author (AK) would evaluate the differences in opinion. The Newcastle-Ottawa Scale (NOS) was utilized to assess the risk of bias of the included studies. Two authors (KR, RKP) independently performed and reported the Newcastle-Ottawa Scale (NOS), differences resolved by discussion and after consultation with the third author (AK). The studies were categorized as: low bias risk (8-9 points), moderate bias risk (5-7 points), and high bias risk (0-4 points).

2.4 Data extraction:

Two authors (SSR, AMF, VDPG) independently performed data extraction from included studied, which was then cross-checked by the third author (AK) to reduce errors. From each included study, the following details were retrieved, the first author's name, the origin country of the analysis, study design, number of COVID-19 patients, median age, gender (female sex proportion), patients with NOAF, data on patients with pre-existing atrial fibrillation if available, ICU admitted patients or patients with respiratory failure, and all-cause mortality. Criteria for severe disease was ICU admission or respiratory failure.

2.5 Statistical Analysis:

MedCalc® Statistical Software version 19.6.4 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) was utilized for all statistical analyses. The random effect model using inverse variance method and DerSimonian and Laird estimator of Tua2 was used to calculate the pooled prevalence and associated 95% confidence interval (CI). Results for outcome analysis were presented as odds ratios (ORs) with 95% CI and pooled using the Mantel-Haenszel random-effects model. The I2 statistics were used to assess the heterogeneity of effect size estimates across included studies (low heterogeneity: I2 [?] 25%; moderate: 25–50%; high > 75%). Publication bias was explored using funnel plots, Egger's regression test, and Begg-Mazumdar's rank correlation test.

3. RESULT:

3.1 Characteristics of the included studies:

The preliminary search reported 1689 articles. Seven hundred thirty-five studies were included after removing duplicates. After considering the title and abstract, 663 articles were eliminated, leaving 72 papers that were regarded as plausible for this analysis. Following review of these studies based on the inclusion and exclusion criteria, 30 articles totaling 81,929 COVID-19 patients were eventually included in this meta-analysis. Table 1 summarizes the baseline characteristics of the included studies.

3.2 Meta-analysis for the prevalence of NOAF in COVID-19 infection:

The overall pooled prevalence of NOAF in patients with COVID-19 across multiple studies was 7.8%, with a 95% confidence interval (CI) ranging from 6.54% to 9.32%. (Figure 2)

3.3 Meta-analysis for Severity Outcome:

The current meta-analysis results indicated that NOAF in the COVID-19 was associated with an increased incidence of severe disease compared with COVID-19 patients without any history of atrial fibrillation (OR= 4.78, 95% CI 3.75 to 6.09). The outcome had high associated heterogeneity (I 2 = 82%). The result was pooled from 15 studies, comprising 54,051 COVID-19 patients (Figure 3 A).

Similarly, our analysis reported that NOAF in COVID-19 patients was associated with an increased incidence of severe disease compared with COVID-19 patients with a history of pre-existing atrial fibrillation (OR=

2.75, 95% CI 2.10 to 3.59). The outcome had moderate associated heterogeneity (I 2 = 41%). The result was pooled from 7 studies, comprising 2625 COVID-19 patients (Figure 3 B).

3.4 Meta-analysis for mortality outcome:

The current meta-analysis results indicated that NOAF in the COVID-19 was associated with an increased mortality compared with COVID-19 patients presenting without NOAF or history of atrial fibrillation (OR= 3.83, 95% CI 2.99 to 4.92). The outcome had high associated heterogeneity (I 2 = 87%). The result was pooled from 25 studies, comprising 56,283 COVID-19 patients (Figure 4 A).

Similarly, our analysis revealed that COVID-19 patients with NOAF had an increased mortality when compared with COVID-19 patients with a history of pre-existing atrial fibrillation (OR= 2.32, 95% CI 1.35 to 3.96). This outcome had high associated heterogeneity (I 2 = 87%). The result was pooled from 13 studies, comprising 3,882 COVID-19 patients (Figure 4 B).

3.6 Risk of bias assessment:

The risk of bias assessment of included observational studies was done with the aid of the Newcastle-Ottawa Scale (NOS). Of 30 studies, 14 were high quality, and 16 were moderate quality, with an average score of 7.4 (Supplementary Table 1). Overall, it was determined that the evidence used in these analyses was of moderate quality.

3.7 Publication Bias:

Visual inspection of the standard funnel plots for all the analyses was identified as having moderate symmetry. With the aid of Egger's regression test and Begg-Mazumdar's rank correlation test, further assessment of publication bias was done. For both these tests, p$<$ 0.05 was considered significant, and the analysis was considered positive for publication bias. No evident publication bias was witnessed for most analyses done in this study. However, Begg-Mazumdar's rank correlation test for NOAF prevalence outcomes had a p $<$ 0.05. The corresponding Egger's regression test showed no evidence of publication bias for this outcome. Hence, the current analyses were without any evidence for publication bias (Supplementary table 2).

4. DISCUSSION:

Our comprehensive meta-analysis reported NOAF to be a major occurrence in patients with COVID-19. Across 30 studies encompassing a total of 81,929 COVID-19 patients, we found the overall pooled random effects estimate of NOAF prevalence to be 7.8% (95% CI: 6.54% to 9.32%). Published literature shows that the prevalence of NOAF in COVID-19 patients ranges from 1% to 19%. ' This finding underscores the importance of monitoring cardiac rhythm in COVID-19 patients. In literature, the incidence of NOAF in surgical and medical mixed intensive care units ranged from 1.7% to 29.5%. However, little information is available regarding the occurrence of NOAF in critically ill COVID-19 patients.

One of the key findings of our analysis was the significant association between NOAF and disease severity in COVID-19 patients. Compared with COVID-19 patients without any history of atrial fibrillation, those who developed NOAF during their illness had a substantially increased risk of severe disease Our analysis also demonstrated that NOAF in COVID-19 patients posed a greater risk of severe disease when compared with patients who had a pre-existing history of atrial fibrillation. Furthermore, a correlation between NOAF and elevated mortality risk in COVID-19 patients was reported in our meta-analysis. NOAF significantly increased the risk of death compared with COVID-19 patients without atrial fibrillation. In addition, our analysis reported that COVID-19 patients with NOAF had a higher mortality risk than those with pre-existing atrial fibrillation. This result suggests that NOAF, a COVID-19 complication, may have unique implications for disease severity beyond what is typically associated with pre-existing atrial fibrillation. This finding emphasizes the need for more focused investigations and further studies to better comprehend the underlying mechanisms causing severe disease among COVID-19 patients with NOAF, potentially guiding customized clinical management strategies for these patients.

Effective clinical management and intervention depend on understanding the pathophysiologic mechanisms underlying NOAF in COVID-19 patients. Even though numerous theories have been put forth, the precise mechanisms causing NOAF in COVID-19 patients are unknown. An extremely inflammatory response brought on by the SARS-CoV-2 virus defines COVID-19. This cytokine storm can result in myocardial injury and disruption of the heart's typical electrical conduction system. Atrial fibrillation pathogenesis has been linked to inflammatory mediators like interleukin-6 (IL-6) and tumor necrosis factor-alpha. Elevated levels of these cytokines in COVID-19 patients may contribute to the development of NOAF by promoting atrial remodeling and electrical instability. Aside from this, the autonomic nervous system is crucial in controlling heart rhythm. Critically ill COVID-19 patients frequently exhibit dysregulation of sympathetic and parasympathetic activity, which can foster the development of NOAF. Hypoxia, stress response, and drugs used for the management of COVID-19 (such as catecholamines) may all cause autonomic dysfunction, leading to NOAF. Further according to recent reports, COVID-19 can cause myocardial injury and ischemia due to various factors, including direct viral damage, micro thrombosis, and hypoxia. These circumstances can affect the atria's electrical stability, creating the perfect environment for atrial fibrillation to start and continue. Myocardial injury may also affect the atrial refractory period and promote reentry circuits, facilitating atrial fibrillation. Viral entry into myocardial cells can disrupt the heart's typical electrical properties, predisposing to atrial fibrillation.' A comprehensive understanding of these mechanisms is essential for developing targeted preventive and therapeutic strategies for NOAF in COVID-19 patients, ultimately improving their clinical outcomes.

It is critical to acknowledge some of the limitations of this meta-analysis. First, we found significant heterogeneity associated with the pooled estimates; as the included studies differed in design, patient characteristics, and location, which may have introduced some variation. The method used for atrial fibrillation surveillance varied across included studies. Strains of SARS-CoV-2 virus, co-morbidities of included patients, vaccination status were not accounted for in the present analysis. The present study didn't account for type of atrial fibrillation based on the duration. Finally this is a study level meta-analysis and hence is limited in its ability to account for heterogeneity observed among the pooled estimate.

In conclusion, our meta-analysis provides valuable insights into the prevalence and clinical implications of NOAF in COVID-19 patients. The results indicate a strong correlation between NOAF and a higher risk of severe illness and mortality among COVID-19. These findings highlight the value of careful surveillance, early detection, and tailored NOAF management strategies among COVID-19 patients to enhance clinical outcomes. Further research is warranted to elucidate the mechanisms underlying this association and guide clinical practice.

5. REFERENCES:

6. Figure legends:

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram

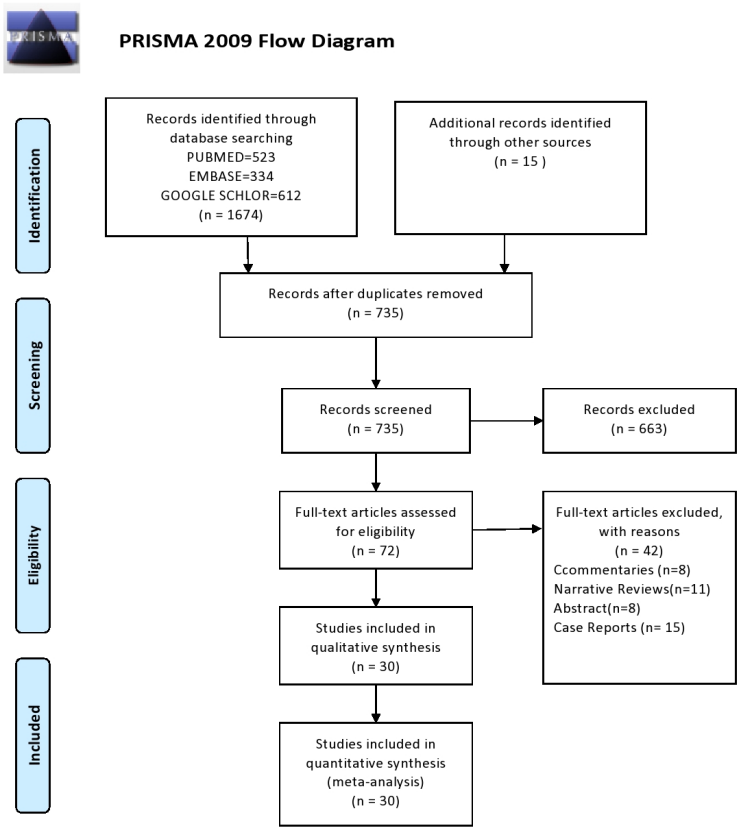
Figure 2: Forest plot for prevalence of NOAF in COVID-19 Patients

Figure 3A: Forest plot for severity of COVID-19 patients among NOAF and without a history of atrial fibrillation as controls

Figure 3B: Forest plot for severity of COVID-19 patients among NOAF and with a history of pre-existing atrial fibrillation as controls

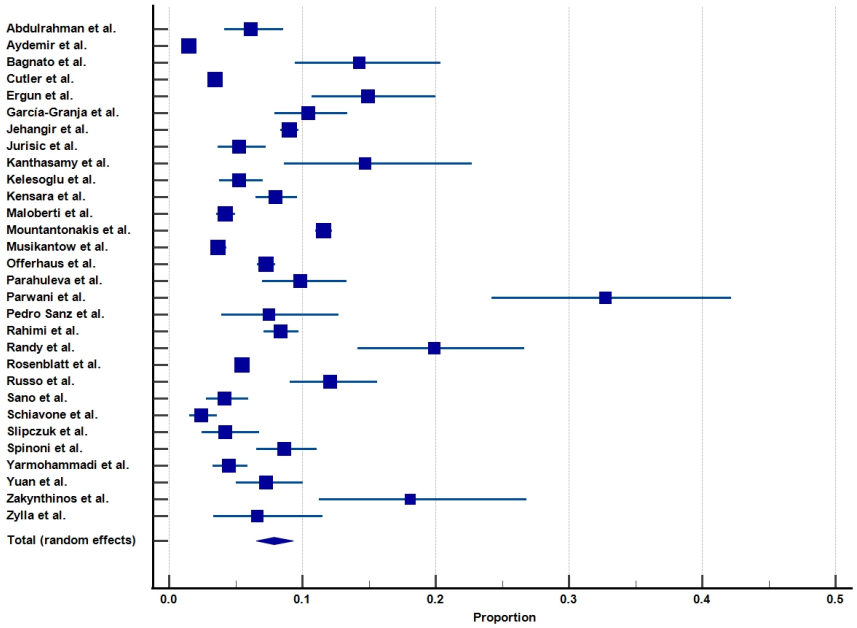
Figure 4A: Forest plot for mortality of COVID-19 patients among NOAF and without a history of atrial fibrillation as controls

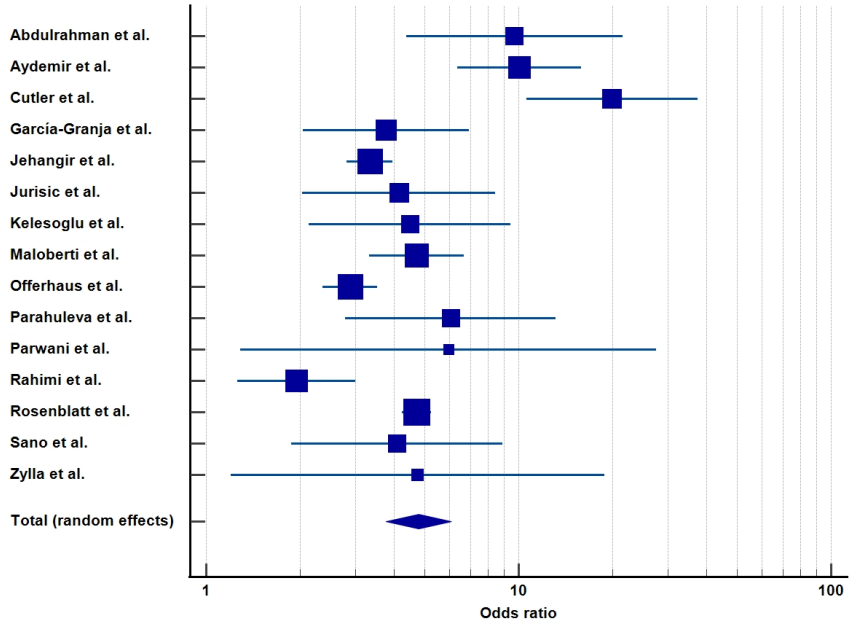
Figure 4B: Forest plot for mortality of COVID-19 patients among NOAF and with a history of pre-existing atrial fibrillation as controls

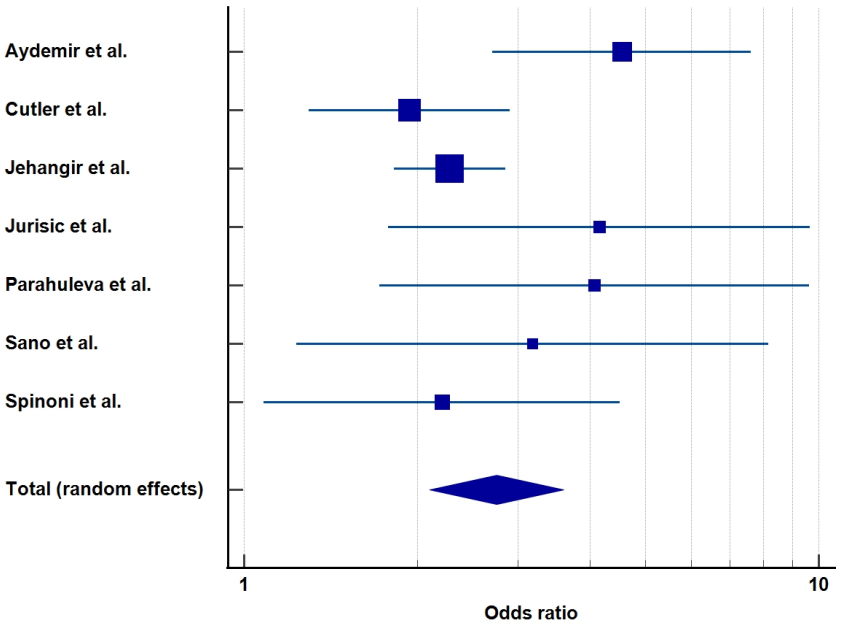


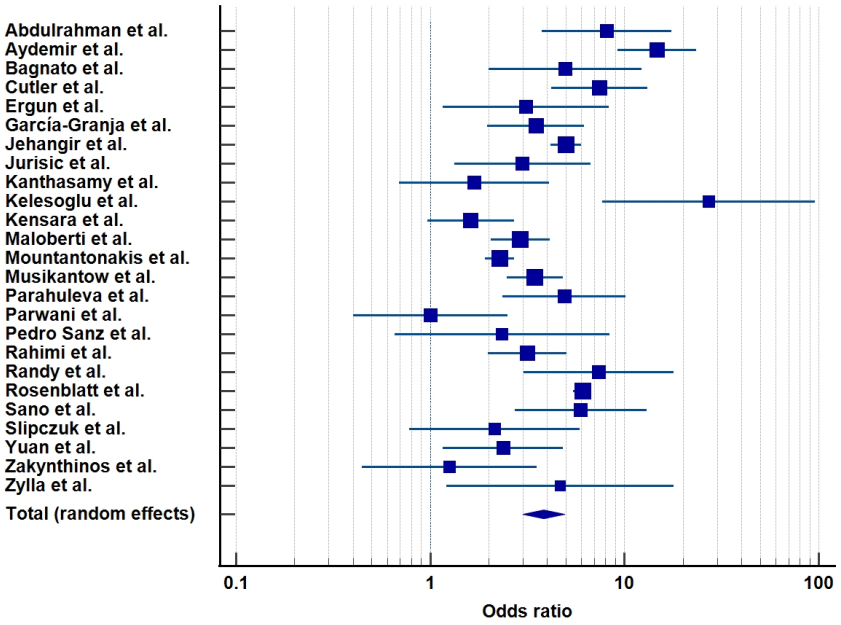
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

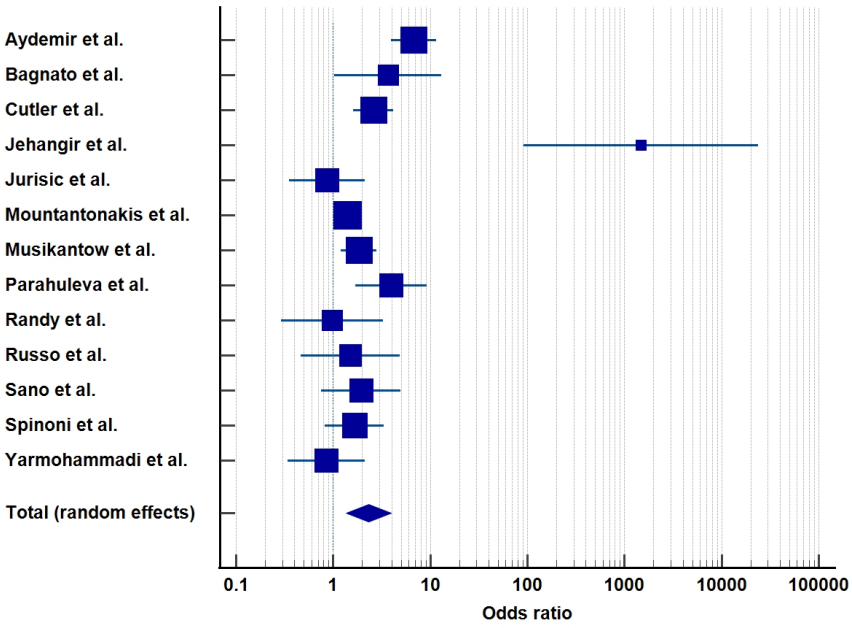
For more information, visit www.prisma-statement.org.











Hosted file

`Table (2).docx` available at https://authorea.com/users/393104/articles/673032-a-systematic-review-and-meta-analysis-of-new-onset-atrial-fibrillation-in-the-context-of-covid-19