



Prevalence of coronary artery disease among COVID-19 patients: a systematic review and meta-analysis

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Abstract

Background: The COVID-19 pandemic has had a profound impact on global health, revealing vulnerabilities in populations with pre-existing conditions. It has placed focus on the intersection of infectious diseases with chronic conditions, notably cardiovascular diseases. These have emerged as significant concerns due to their potential to exacerbate COVID-19 outcomes.

Objective: To estimate the prevalence of coronary artery disease (CAD) among COVID-19 patients.

Methods: In this systematic review and meta-analysis, an extensive literature search was conducted in seven databases and preprint servers till 2023-04-13 as per a pre-registered protocol (CRD42022367501). Primary studies reporting CAD among COVID-19 patients were included. Individual study estimates were pooled using the random-effects model due to the heterogeneity. Prediction interval was used to identify the range into which future studies are expected to fall. Subgroup analysis and meta-regression were done to reduce heterogeneity, followed by publication bias and quality assessments.

Results: 33 studies with 40,064 COVID-19 patients revealed a pooled prevalence of coronary artery disease of 15.24% (95% CI: 11.41% - 20.06%). The 95% prediction interval ranged from 2.49% to 55.90%. The studies were highly heterogeneous ($\tau^2=0.89$), and subgroup analysis significantly reduced it ($P=.002$). Europe reported the highest prevalence [21.70% (14.80% - 30.65%)], and Asia has the least prevalence [10.07% (6.55% - 15.19%)]. A symmetric doi plot and an LFK index of 0.57 revealed no evidence of publication bias.

Conclusions: The substantial prevalence of CAD among COVID-19 patients underscores the need for high clinical vigilance. The geographical disparities suggest potential regional differences in healthcare infrastructure, genetic predispositions, or lifestyle factors that warrant further investigation. The findings emphasize the importance of routine cardiac assessments for COVID-19 patients for timely interventions and better patient outcomes.

Keywords: Coronary artery disease, COVID-19, Ischaemic heart disease, Myocardial infarction, Heart attack, Systematic Review, Meta-analysis, Angina pectoris, Coronavirus, Evidence Synthesis



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Evidence in Context

Prior Evidence: Throughout the COVID-19 pandemic, there have been several reports of several noncommunicable diseases including cardiovascular diseases co-occurring with COVID-19. There is a lack of summarised evidence on coronary artery disease in COVID-19 patients.

Evidence added by this study: The prevalence of coronary artery disease among COVID-19 patients is 15%. It shows considerable variation with geography, with a higher prevalence in Europe (22%), and a lower prevalence in Asia (10%).

To view Article



Introduction

The COVID-19 pandemic has posed unprecedented challenges to global public health and the entire healthcare system[1]. According to the World Health Organization emergency diseases dashboard 2022, the cases have reached over 769 million globally till 06th December 2022[2]. It hardly took any time to be a major public health issue, and due to the lack of available treatment, the transmission of disease also became easier. The increased burden due to coexisting cardiovascular diseases has been a leading concern in this pandemic[1].

It is suggested that COVID-19 can be associated with other co-morbidities[3]. Some studies also reveal that COVID-19 infection affects older populations with existing co-morbid conditions more[4, 5]. The major and most prevalent co-morbidities identified among COVID-19 cases were cardiovascular diseases, diabetes and hypertension, which are also linked with SARS-CoV-2[6]. There is a significant focus on its association with cardiovascular diseases, particularly coronary artery disease (CAD)[7].

As the COVID-19 pandemic progressed with increased mortality and morbidity, their related complications were also visible. The COVID-19 pandemic, along with respiratory failure, gave rise to cardiological complications. Studies have revealed that the prevalence of cardiovascular diseases was high during the COVID-19 surge[6, 8]. Research conducted during the Intensive Care Unit (ICU) admissions also revealed the difficulty in recovery of patients with existing cardiovascular complications like coronary artery disease, heart failure and stroke, and myocardial and atherosclerosis conditions [9]. One study conducted in China also revealed that myocardial infarction or cardiovascular injury among patients suffering from COVID-19 increases the chances of death[10]. A recent observational study conducted at global levels has shown high coagulation and thrombotic events rates among COVID-19 patients admitted to Intensive care units[11]. The consequences of heart failure and other inflammation-type responses, despite not having any prior history have also been observed[12]. Several studies have also indicated that the impact of SARS-CoV-2 actually doubled due to cardiovascular complications, which made life more difficult and mortality more prevalent[13]. History of heart failure or the existence of heart failure events leading to coronary artery disease may complicate the situation and make management and prognosis even more challenging[14, 15].

Given the growing concerns among epidemiologists and physicians, this study seeks to assess the prevalence of coronary artery disease (CAD) in COVID-19 patients to provide a comprehensive understanding of the extent to which CAD is common among those afflicted with COVID-19.

Materials & Methods

Search strategy and selection criteria

We searched seven databases: PubMed, Scopus, Web of Science, ProQuest, EMBASE, EBSCO Host, and Cochrane. The pre-print servers (medRxiv, arXiv, bioRxiv, BioRN, ChiRxiv, ChiRN and SSRN) are also included in our search strategy [Table S1]. Furthermore, new eligible studies were extracted by carefully searching for relevant references from included papers and other suitable reviews. The primary outcome was the prevalence of coronary artery disease among COVID-19 patients. The study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42022367501.

The search keywords included 'coronary disease', 'COVID-19', and other synonymous words. MeSH terms, and terms with an asterisk were used to identify related articles in the study title [Table S1]. Articles were saved in Mendeley Desktop V1.19.5 software to manage citations, remove duplicates, and facilitate the review process.

Data extraction and management

Two authors (NA, NCG) individually reviewed each paper. The disagreement regarding the selection of article, was resolved between two of the co-authors who conversed to build consensus and agreement. Any conflict between the two leading reviewers about the eligibility of the publication, a third co-author (MAS) was consulted to assess the article and help choose whether to include the study. The reviewers discovered five articles were relevant to the main topic. Then from the eligible articles, the following information was gathered from each source article: the author's name, the place where the study was conducted, the year of publication, the study design, the number of COVID-19 cases, cases of coronary artery disease, and other important details. A data extraction table has been prepared in a Microsoft Excel spreadsheet for further analysis.

The articles searched were reported according to the PRISMA checklist (Preferred Reporting Standard of Systematic Reviews and Meta-Analysis) to ensure scientific precision [Table S2]. In addition, the reviewers thoroughly read all of these publications before composing their conclusions.

Quality Assessment

The studies were independently rated by two authors using the study quality assessment tools as recommended by the National Institute of Health [Table S3].

Inclusion and Exclusion Criteria

All articles published until 13th of April 2023 were considered for this study. The inclusion and exclusion criteria have been given in [Table S4].

Data Analysis

The prevalence of coronary artery disease among COVID-19 patients was calculated by dividing the number of cases of coronary artery disease by the total number of study participants. The proportions were transformed to the logarithmic scale. These were then synthesised using a random intercept logistic regression model[16]. To describe the variance amongst studies, the heterogeneity of the studies evaluated in the meta-analysis was assessed using the I^2 test[17], in addition to the prediction interval[18], tau, tau-squared[19], and Cochran's Q[20]. Heterogeneity was classified as low, moderate, and high, respectively, based on I^2 values of less than 25%, 25-50%, and more than 50%. Therefore, the articles that were included in the meta-analysis were very heterogeneous. A 95% confidence interval using a random effect was used to evaluate the overall effect since we anticipated considerable between-study heterogeneity and it was seen to be higher too. $P < .05$ has been considered statistically significant. For the assessment of publication bias and small-study effects, we used Doi plot and the accompanying LFK index since this is a meta-analysis of proportions[18]. We performed a subgroup analysis based upon geography (continent) of study population. 'meta' and 'metafor' packages in R version 4.2.1 were utilized for conducting the meta-analysis.

Results

The systematic search was initially performed on 30th November, 2022 and repeated on 13th April, 2022. It yielded 510 articles, among which 137 duplicates were detected and removed. Two investigators (NA & NCG) independently reviewed the title/abstract screening of the 373 articles, and 311 were removed. Additionally, several articles were identified by checking the reference list of included studies, references in relevant reviews, forward citation for eligible studies, a search in Google Scholar (not a primary database for systematic reviews), and seeking the opinion of experts in the field. Full text screening of all these selected records yielded 33 studies for inclusion in systematic review and meta-analysis[7, 21–52]. The PRISMA flow chart depicts the article selection and selection process.

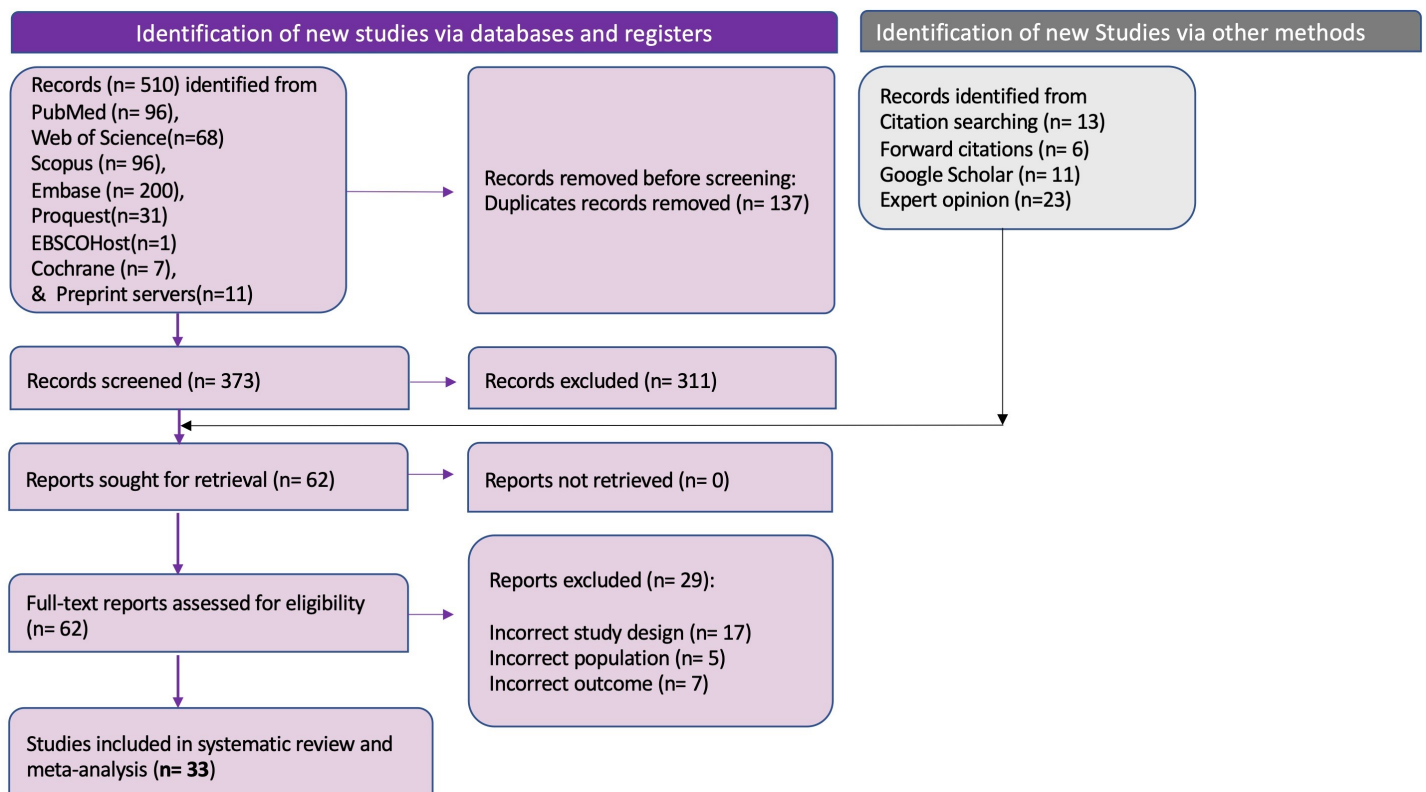


Figure 1. PRISMA flow chart for included studies in systematic review and meta-analysis of prevalence of coronary artery disease among COVID-19 patients

15 of the 33 studies (45.45%) were conducted in Asia, 12 of the 33 (36.36%) in Europe, and 5 (15.15%) took place in North America. This study pooled data from several countries across the globe[41]. The baseline characteristics of all the studies has been given in **Table 1**.

Table 1: Brief summary of the studies featured in the meta-analysis (N=33)

Authors	Country	Study Design	Number of eligible patients	Coronary artery disease
Xie et al.(2020)	China	Retrospective study	62	53.23%
Aladağ et al.(2020)	Turkey	Cross-sectional study	50	44.00%
Barman et al.(2021)	Turkey	Retrospective study	607	19.11%
Bruce et al.(2020)	United kingdom	Cross-sectional study	1222	22.34%
Cen et al.(2020)	China	Cohort study	1007	6.45%
Gupta et al.(2020)	India	Retrospective study	200	4.50%
Hewitt et al.(2020)	United kingdom and Italy	Cohort study	1564	22.06%
Iaccarino et al.(2020)	Italy	Cohort study	1591	13.58%
Lagi et al.(2020)	Italy	Cohort study	84	14.29%
Lendorf et al.(2020)	Denmark	Retrospective study	111	17.12%
Li et al.(2020)	China	Retrospective study	74	8.11%
Liao et al.(2020)	China	Retrospective study	56	7.14%
Turagam et al.(2020)	United states	Retrospective cohort study	140	25.00%
Argenziano et al.(2020)	United states	Retrospective study	1000	13.10%
Chen et al.(2020)	China	Retrospective cohort study	35	22.86%
Deng et al.(2020)	China	Retrospective study	112	13.39%
Xingwei et al.(2020)	China	Retrospective study	54	14.81%
Lodigiani et al.(2020)	Italy	Retrospective cohort study	388	13.92%
Shi et al.(2020)	China	Retrospective study	671	8.94%
Tai et al.(2020)	China	Retrospective cohort study	332	3.31%
Rossi et al.(2020)	Italy	Cohort study	1075	10.70%
Lax et al.(2020)	Austria	Prospective study	11	27.27%
Inciari et al.(2020)	Italy	Case-control	99	16.16%
Zhang et al.(2020)	China	Cross-sectional study	140	5.00%
Richardson et al.(2020)	United states	Case series	5700	10.44%
Zhang et al.(2020)	China	Cross-sectional study	143	11.89%
Du et al.(2020)	China	Retrospective study	85	11.76%
Scoccia et al.(2021)	Italy	Retrospective study	1625	68.92%
Jamora et al., (2022)	Philippines	Retrospective cohort study	10,881	3.90%
Bali et al. (2021)	India	Retrospective cohort study	120	25.00%
Meloche et al, (2021)	USA	Pospective study	5019	13.51%
Slipczuk et al, (2021)	USA	Retrospective cohort study	493	60.04%
Prabhakaran et al. (2021)	Multinational	Cohort study	5313	10.92%

It mentions the authors, site of study, sample size, prevalence of coronary artery disease among COVID-19 patients, and other key details. This Italian study [44] reported the highest prevalence (68.92%) while the least prevalence (3.90%) was found in this study in Phillipines[33].

Pooled prevalence

Amongst the 33 studies reporting on the prevalence of coronary artery disease among COVID-19 patients, we computed the pooled prevalence. It came to be 15.24% (95% CI: 11.41% - 20.06%). The prediction interval depicts the range into which future studies exploring the same outcome are expected to report. This prediction interval ranged from 2.49% to 55.90%.

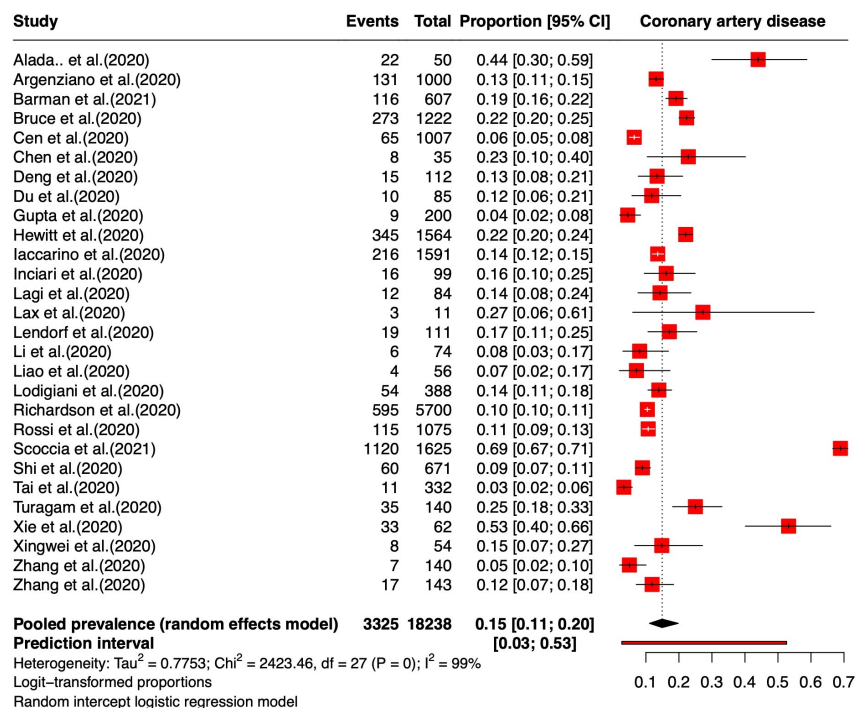


Figure 2. Pooled prevalence forest plot of coronary artery disease among COVID-19 patients.

Heterogeneity estimation and exploration

The individual study estimates showed considerable heterogeneity with an I^2 of 98.9% (95% CI: 98.7% - 99.0 %), and a tau-squared of 0.89. The Cochran's Q is also significant with a value by Wald's test of 4192.02 ($P < .001$). We used a random-effects model for the meta-analysis due to this high heterogeneity. To reduce this heterogeneity, we performed subgroup analysis and meta-regression.

Subgroup analyses based upon geographical criteria reduced heterogeneity. Dividing the studies into continents resulted in three subgroups. There is a significant difference between the three continents. This can be seen in the result of the test of moderators ($Q = 14.77$, $df = 3$, $P = .002$). Europe reported the highest prevalence [21.70% (14.80% - 30.65%)], and Asia has the least prevalence [10.07% (6.55% - 15.19%)]. Subgrouping also reduced the heterogeneity in the individual subgroups. Details of the subgroup analysis is given in **Table 2**.

Table 2: Subgroup analysis for pooled prevalence of coronary artery disease among COVID-19 patients – based on continent

Sub-group	No. of studies	Pooled estimate (95% CI)	tau2	p value
Continent				$P = .002$
Asia	15	10.07% (6.55% - 15.19%)	0.76	
Europe	12	21.70% (14.80% - 30.65%)	0.62	
North America	5	21.02% (10.48% - 37.68%)	0.87	
Multinational	1	10.92% (10.11% - 11.78%)	-	

We conducted meta-regression based upon the sample size of individual studies. This was not significant ($P = .11$). We constructed a bubble plot to visualize the same.

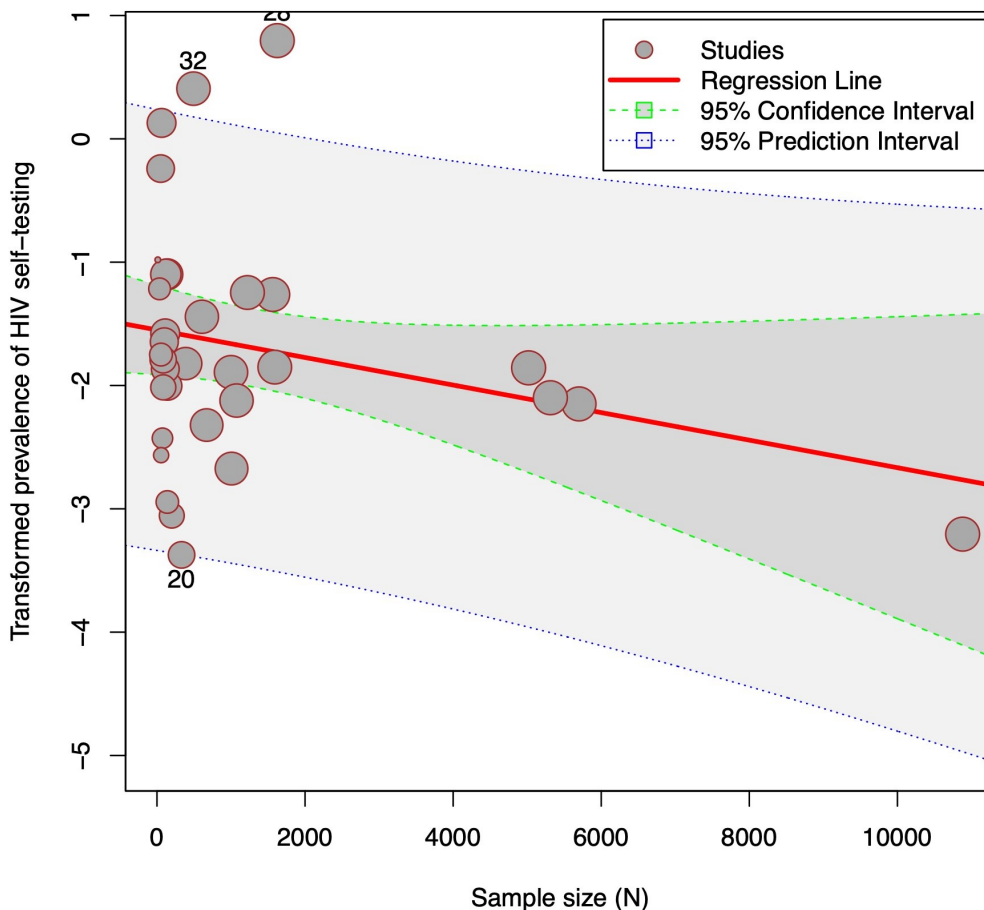


Figure 3. Bubble plot based on the prevalence of coronary artery disease among COVID-19 patients

Assessment of publication bias and small-study effects

We used a Doi plot and the accompanying LFK index to assess publication bias and small study effects. The Doi plot showing individual study estimates against a folded quantile plot can be seen in **Figure 4**. The LFK index is 0.57. This does not suggest publication bias for estimation of prevalence of coronary artery disease among COVID-19 patients.

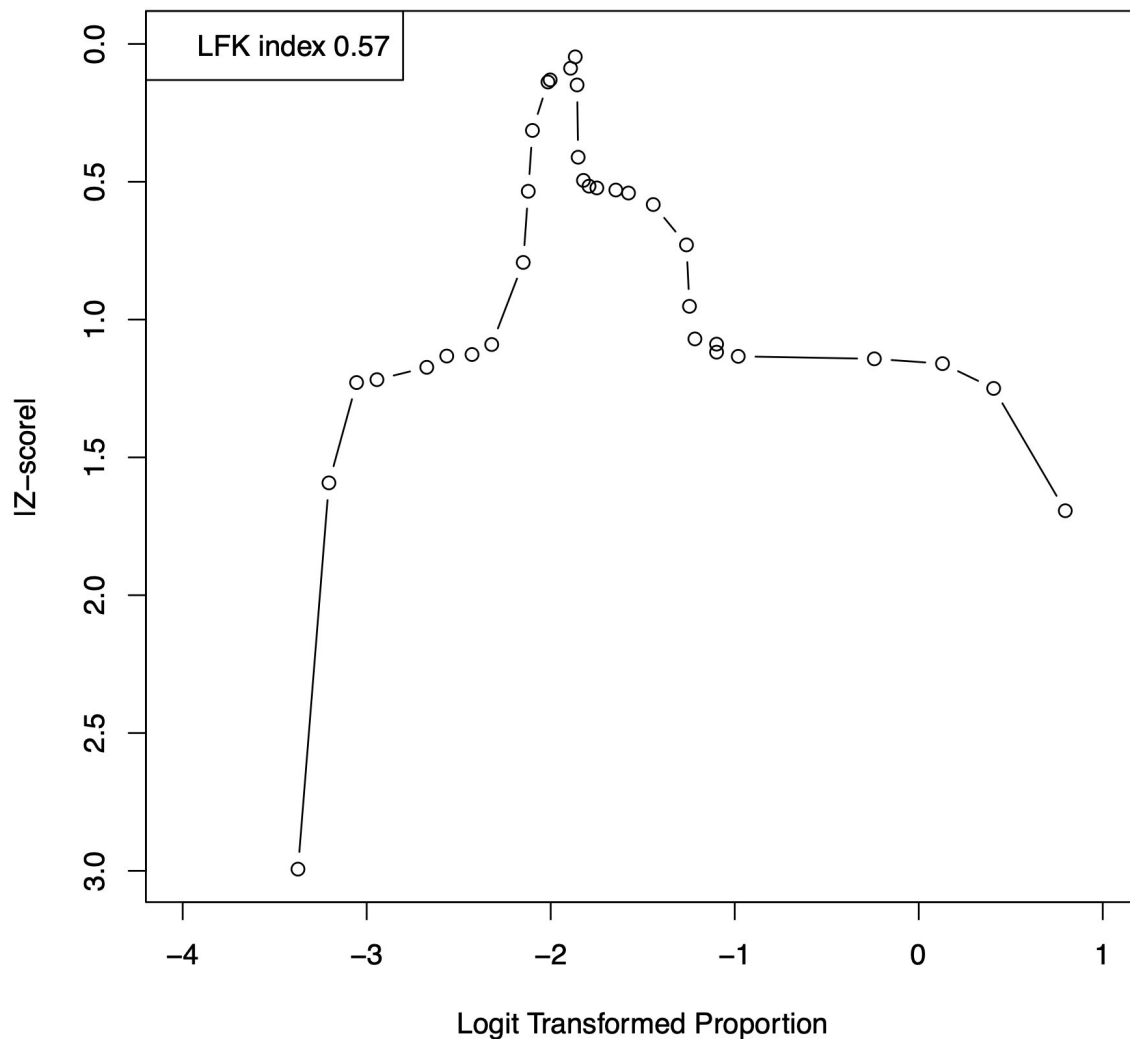


Figure 4. Doi plot and LFK index to assess publication bias and small-study effects for prevalence of coronary artery disease among COVID-19 patients.

Risk of Bias Assessment

The quality assessment of the findings of the included study is illustrated in the supplement file [Table S2], with majority rated to have fair quality. The assessment of quality of the included studies can be checked in the supplementary file [Table S2], with most studies (32 out of 33) having fair quality, while one of the studies being poor in quality. Excluding Barman et al., (2021), the only study with a poor quality slightly reduced the pooled prevalence from 15.24% (95% CI: 11.41% - 20.06%) to 14.77% (95% CI: 10.84% - 19.81%) [Figure S1].

Discussion

This systematic review and meta-analysis results indicate that coronary artery disease is highly prevalent with COVID-19. The pooled prevalence is 15.24% (95% CI: 11.41% - 20.06%), and varies by geography. It is higher in Europe [21.70% (14.80% - 30.65%)], and lower in Asia [10.07% (6.55% - 15.19%)].

The pooled prevalence of CAD among COVID-19 patients of 15.24% is a significant figure, considering the vast number of COVID-19 cases globally. The World Health Organization reported over 769 million cases of COVID-19 by August 2023[2]. If we extrapolate the prevalence data, it suggests that a staggering number of these patients might have CAD, emphasizing the importance of understanding this association for better clinical management.

There is notable heterogeneity in the studies. The significant variation in CAD prevalence across different continents, with Europe reporting the highest prevalence and Asia the least, could be attributed to multiple factors. Differences in healthcare infrastructure, diagnostic capabilities, genetic predispositions, lifestyle factors, and the prevalence of other co-morbidities might play a role[54]. For instance, Europe has an aging population with a higher prevalence of cardiovascular diseases, which might contribute to the higher observed prevalence of CAD among COVID-19 patients[55].

There has been well-established documentation for the association between COVID-19 and cardiovascular complications. Previous studies have highlighted that COVID-19 can exacerbate underlying cardiovascular conditions and even lead to new-onset cardiac complications[56]. The virus's ability to induce a hyperinflammatory state, coupled with its direct and indirect effects on the cardiovascular system, can lead to myocardial injury, arrhythmias, and thromboembolic events. This is particularly concerning for patients with pre-existing CAD, as this study from China indicated that myocardial injury among COVID-19 patients significantly increases the risk of death[57].

In a cohort study involving 1007 individuals with mild to moderate COVID-19 from three Wuhan hospitals, the risk factors for disease progression were investigated. Over a 28-day follow-up, 71.50% of patients remained stable or recovered, while 22.05% progressed to severe disease, 2.18% became critically ill, and 4.27% died. Factors significantly associated with disease progression included age over 65, male gender, and pre-existing conditions such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and coronary artery disease. Notably, the presence of coronary artery disease was identified as a significant risk factor for disease progression, with a hazard ratio (HR) of 1.83 (95% CI 1.26–2.66)[25].

Several studies show cardiovascular conditions such as coronary heart disease are associated with increased risk for severe COVID-19 and mortality, hence investigating the coronary heart disease prevalence can help stakeholders prioritize cardiovascular disease healthcare resources[41]. This study identifies evidences from different geographical locations which gives an insight into the disease complications across the world[31]. A study conducted in China among 332 COVID-19 patients suggests of 48 of cardiovascular patients around 23 showed disease severity and required immediated ICU admission[47]. Similarly a prognosis of cardiac injury was checked among the COVID19 patients acute respiratory distress were also high among the patients suffering with cardiac injury[7]. Another study conducted among 62 patients out of with 33 had cardio vascular diseases and 3.2 % of them reached severity of infection and were put under ventillators[49]. Some studies also show the inverse relationship among the two as COVID-19 and cardiovascular conditions such as stroke. A study conducted in Phillipines among 10,881 COVID-19 patients shows 3.4% of incidence of stroke among patients with COVID-19 which resulted in increased ICU admissions and even deaths[33]. Some studies conducted in the past also reveal SARS CoV-2 as the major precursor which invades cardic cells thereby leading to cardiovasuclr conditions like myocardial inflammation and coronary arthey disease[58].

We need to increase the awareness regarding the importance of routine cardiac screening for COVID-19 patients. Early detection of CAD can lead to timely interventions, optimizing the management of these patients. This is particularly crucial given the observed complications in COVID-19 patients with cardiovascular diseases, such as increased ICU admissions and challenges in recovery[56].

As the pandemic continues to evolve, it's imperative for clinicians to be vigilant about cardiovascular complications in COVID-19 patients. Further research is needed to elucidate the mechanisms underlying this association and to develop strategies to mitigate the risks associated with it. There is need for vigorous research in these topics and future research can be conducted for multiple cardiovascular diseases through sub-grouping of complications like myocardial infraction, atherosclerosis, thrombosis, heart failure and stroke. The area explored in this study has remain specific to coronary artery disease which gives futher scope for exploring other cardiovascular conditions in a similar manner or different. These findings would enable the healthcare providers, researchers and policy makers to more accurately assess the issue, identify the threats in this area and develop strategies to accomplish them.

This is a well-conducted systematic review and meta-analysis that summarised the pooled prevalence of CAD among COVID-19 patients and explores the observed heterogeneity, with robust methods for publication bias assessment. While we could not detect any evidence of small-study effects, it's essential to consider the limitations. The significant heterogeneity observed, even though reduced through subgroup analysis, suggests that individual study characteristics might influence the reported prevalence. Additionally, the quality assessment revealed that most studies were of fair quality, with one being of poor quality. This emphasizes the need for more high-quality research to provide a clearer picture of the association between CAD and COVID-19.

Conclusions

This systematic review and meta-analysis examined 40,064 individuals from 33 studies and found 5333 patients with coronary artery disease in COVID-19 patients. The overall pooled prevalence of coronary artery disease in COVID-19 is 15.24%. Given the high prevalence, there is a necessity to routinely assess cardiac health of COVID-19 patients admitted in the hospital. The association between the two conditions has profound implications for patient management and outcomes.

Supporting information

None

Ethical Considerations

None

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Author contribution statement

Naushaba Akhtar: Conceptualization (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal). **Nandhni Chiruganam Gandhi:** conceptualization, Software (lead); writing – review and editing (equal). **Gladius Jennifer:** Methodology (lead); writing – review and editing (equal). **Sanghamitra Pati:** Conceptualization (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal).

Data availability statement

All data generated or analyzed during this study are included in this published article [and its supplementary information files]. A preprint version is available at <https://doi.org/10.1101/2023.06.01.23290768>

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflicts of Interest

None of the authors has declared any competing interests.

Supplementary material

Table S1: Adjusted search terms as per searched electronic databases.

Table S2: PRISMA checklist for reporting of the systematic review and meta-analysis

Table S3: Quality assessment of included studies.

Table S4: Inclusion and Exclusion Criteria

Figure S1: Sensitivity analysis excluding a poor quality study.

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