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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 significantly affected worldwide health, highlighting weaknesses in individuals with pre-existing medical conditions. This situation has underscored the relationship between infectious diseases and chronic health issues, particularly cardiovascular diseases. The latter have become a major focus, as they can worsen the outcomes of COVID-19 infections. This study aims to evaluate the coronary artery disease (CAD) prevalence in individuals diagnosed with COVID-19.

Methods: This systematic review involved a literature search across seven databases and preprint servers up to April 13, 2023, following a pre-registered protocol (CRD42022367501). It focused on primary studies that reported on CAD in COVID-19 patients. Due to the variability among studies, a random-effects model was employed to aggregate individual study estimates. To address heterogeneity, subgroup analysis and meta-regression were conducted. Additionally, assessments of publication bias and the quality of the studies were carried out.

Results: The meta-analysis of 33 studies encompassing 40,064 individuals with COVID-19 found a combined prevalence of CAD at 15.24% with 95% CI: 11.41% to 20.06%. A prediction interval for this prevalence spanned from 2.49% to 55.90%. These studies exhibited high heterogeneity, with a tau-squared value of 0.89. However, subgroup analysis significantly mitigated this heterogeneity (P=.002). The CAD prevalence in COVID-19 patients was highest in Europe at 21.70% (95% CI: 14.80% - 30.65%) and lowest in Asia at 10.07% (95% CI: 6.55% - 15.19%). Doi plot suggested no significant publication bias among these studies (LFK index=0.57)

Conclusions: The notable CAD prevalence in COVID-19 patients highlights the necessity for heightened clinical vigilance. The observed geographical variations in prevalence point to possible differences in regional healthcare infrastructure, genetic predispositions, or lifestyle factors, meriting deeper research. These results underscore the critical importance of conducting routine cardiac evaluations in COVID-19 patients, enabling timely medical interventions and ultimately leading to improved patient outcomes.

Keywords: *covid-19, coronary artery disease, systematic review, meta-analysis, myocardial infarction, ischaemic heart disease, heart attack, angina pectoris, evidence synthesis, coronavirus*

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Evidence in Context

• COVID-19 significantly increases the risk of coronary artery disease (CAD) in patients. • The combined prevalence of CAD in COVID-19 patients is 15.24%. • CAD prevalence is highest in Europe (21.70%) and lowest in Asia (10.07%). • COVID-19 patients with CAD have higher mortality risks. • Targeted care and further research are essential.

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Introduction

The COVID-19 global health crisis, as declared by the World Health Organization (WHO), has significantly affected healthcare systems and public health worldwide, with over 769 million cases reported by December 6, 2022 [1-2]. The rapid evolution of COVID-19 into a critical public health emergency, especially in the absence of initial effective treatments, led to its widespread transmission. One notable challenge during this pandemic has been its amplified impact on patients with existing cardiovascular conditions [1].

Research has identified a potential association between COVID-19 and various comorbidities. Particularly at risk are older individuals with pre-existing health conditions, as emphasized by several studies [3-5]. Among the most prevalent comorbidities in COVID-19 patients are cardiovascular diseases, diabetes, and hypertension [6]. The connection between COVID-19 and cardiovascular complications, particularly coronary artery disease (CAD), is a significant concern [7].

As the pandemic's severity escalated, its effects on mortality and morbidity, including a range of complications, became more evident. The pandemic's impact extended to the emergence of cardiac issues alongside respiratory distress. Studies have consistently reported increased cardiovascular conditions coinciding with COVID-19 case surges [6-8]. Observational studies globally have noted that In COVID-19 patients, especially those in Intensive Care Units (ICU), there is a notable occurrence of coagulation and thrombotic events [11]. These studies have underscored the complexity of recovery for patients with pre-existing cardiac problems such as heart failure , CAD, stroke, atherosclerosis, and myocardial infarction [9]. Notably, cardiovascular injuries, including myocardial infarction in COVID-19 patients, have been linked to increased mortality risks [10]. Even in patients without a prior cardiac history, instances of heart failure and inflammatory responses have been observed [12]. The exacerbation of cardiovascular complications due to SARS-CoV-2 infection suggests a link to higher mortality rates [13]. The presence of heart failure or prior heart failure incidents further complicates the management and prognosis of patients with CAD [14, 15].

Given these concerns, our research aims to assess the overall prevalence of CAD in individuals diagnosed with COVID-19, highlighting a critical aspect of the pandemic's impact on public health.

Materials & Methods

The Protocol of this systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO), bearing the registration number CRD42022367501.

Search strategy and selection criteria

A literature search across several databases, namely Scopus, PubMed, ProQuest, EMBASE, EBSCO Host, Web of Science, and the Cochrane Library was performed. Additionally, we extended our search to include pre-print servers such as BioRN, SSRN, ChiRxiv, ChiRN, arXiv, bioRxiv, and medRxiv. To enhance the scope of our study, we meticulously reviewed references from the selected articles and other relevant review papers to identify new studies meeting our criteria. Our search strategy employed key phrases such as 'coronary disease' and 'COVID-19', along with their synonyms. We utilized MeSH (Medical Subject Headings) terms and applied wildcard asterisks to capture relevant variations in the study titles **[Table S1]**. For efficient citation management and to streamline the review process, we utilized Mendeley Desktop V1.19.5 software. This tool was instrumental in organizing the articles, eliminating duplicate entries, and facilitating a smooth review workflow.

Data extraction and management

The process of article screening for inclusion in our study was individually undertaken by two authors, NA and NCG. Whenever there were disagreements between the two co-authors about including an article, they engaged in discussions to reach a consensus. If these primary reviewers were unable to agree on the eligibility of a specific publication, they consulted a third co-author, MAS, for an additional evaluation. During this process, we identified five articles relevant to our research topic. For each article, we meticulously collected comprehensive information, including the author(s) names, the study's geographic location, publication year, number of COVID-19 cases, the incidence of CAD cases, the study design, and other relevant data. We systematically organized this data into a table for extraction, using Microsoft Excel to enable efficient analysis. Additionally, To ensure a comprehensive and well-informed review, the authors thoroughly read all the selected publications before finalizing their conclusions. In our commitment to maintaining the highest standards of scientific accuracy, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, as outlined in **Table S2**. Moreover, to ensure a thorough and informed review, all authors meticulously read each selected publication in its entirety before finalizing their conclusions.

Quality Appraisal

The quality evaluation of the studies was carried out by two separate reviewers, utilizing the assessment tools developed by the National Institutes of Health (NIH) **[Table S3]**.

Eligibility criteria

For this study, we considered all articles published up until April 13, 2023. The specific criteria for inclusion and exclusion for the study are detailed in **Table S4**.

Data Analysis

The meta-analysis was conducted to aggregate the overall prevalence of CAD, taking into account the number of participants diagnosed with CAD and the total number of COVID-19 patients in each study. We synthesized this data using a random effect model [16]. We utilized various statistical methods, including I2 metrics [17], the prediction interval [18], tau squared [19] and Cochran's Q [20] to assess the heterogeneity. Heterogeneity in the studies was regarded as low, moderate, or high, depending on the I2 metrics being under 25%, between 25-50%, and more than 50%, respectively. Statistical significance was set at $P<0.05$. For detecting publication bias statistically, we employed the Doi plot and LFK index, which are particularly relevant for meta-analyses of proportions [18]. Additionally, we conducted a subgroup analysis based on the geographic location (continent) of the study populations. The meta-analysis was performed using the R statistical software (V 4.2.1).

Results

The initial systematic search was conducted on 30th November 2022 and subsequently updated on 13th April 2022. This search resulted in the identification of 510 articles. Of these, 137 were found to be duplicates and were subsequently removed. The remaining 373 articles underwent title and abstract screening by two independent investigators, NA and NCG, resulting in the exclusion of 311 articles. In addition to the database search, several other strategies were employed to ensure a comprehensive review. These included examining the reference lists of the studies that were included, reviewing references cited in relevant review articles, searching citations utilizing Google Scholar and consulting with experts in the field for their recommendations. After a thorough full-text examination of all the selected studies, 33 studies has been ultimately included in this systematic review and meta-analysis [7, 21–52]. Table 1 details the characteristics and geographical distribution of the 33 studies included in this meta-analysis. The process of study selection and the results at each stage are detailed in the PRISMA flow chart **[Figure 1].**

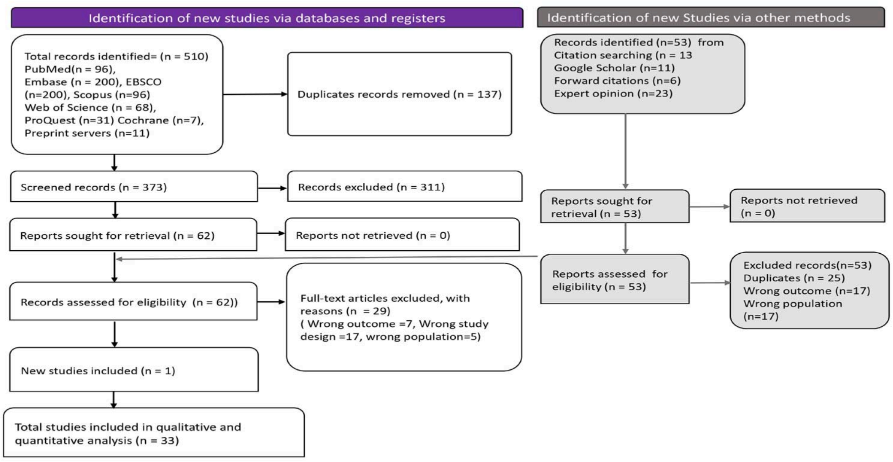

Figure 1: PRISMA flow diagram presenting the selection process of the studies

Table 1: Characteristics of included studies (K=33)

Study	Geography (continent)	Sample	Event (%)
Xie	Asia	62	53.23
Aladağ	Europe	50	44.00
Barman	Europe	607	19.11
Bruce	Europe	1222	22.34
Cen	Asia	1007	6.45
Gupta	Asia	200	4.50
Hewitt	Europe	1564	22.06
Iaccarino	Europe	1591	13.58
Lagi	Europe	84	14.29
Lendorf	Europe	111	17.12
Li	Asia	74	8.11
Liao	Asia	56	7.14
Turagam	North America	140	25.00
Argenziano	North America	1000	13.10
Chen	Asia	35	22.86
Deng	Asia	112	13.39
Xingwei	Asia	54	14.81
Lodigiani	Europe	388	13.92
Shi	Asia	671	8.94
Tai	Asia	332	3.31
Rossi	Europe	1075	10.70
Lax	Europe	11	27.27
Inciari	Europe	99	16.16
Zhang	Asia	140	5.00
Richardson	North America	5700	10.44
Zhang	Asia	143	11.89
Du	Asia	85	11.76
Scoccia	Europe	1625	68.92
Jamora	Asia	10,881	3.90
Bali	Asia	120	25.00
Meloche	North America	5019	13.51
Slipczuk	North America	493	60.04
Prabhakaran	Multinational	5313	10.92

Out of the 33 studies included, a significant portion, 15 studies (45.45%), were conducted in Asia. Europe accounted for 12 of the 33 studies (36.36%), while North America was the setting for 5 studies (15.15%) **[Table 2].** This diverse collection of studies provided a global perspective, pooling data from various nations in the world [41]. The important features of these studies, including their geographic distribution, participant demographics, and author names, prevalence of CAD in COVID-19 patients, sample size, site of study, and other key details are outlined in **Table S5**. In our analysis, the study conducted in Italy [44] reported the highest prevalence of CAD in among COVID-19 population, with a rate of 68.92%. On the other hand, the lowest prevalence was observed in a study from the Philippines [33], where the prevalence was found to be 3.90%.

Table 2: Subgroup analysis based on geographical location

Geography	No. of studies	Pooled estimate (95% CI)	Tau^2
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)	-

Meta-analysis

From the 33 studies that investigated the reported CAD cases among COVID-19 patients, we calculated an overall prevalence rate. The combined prevalence of CAD in these studies was found to be 15.24% (95% CI: 11.41% to 20.06%). This pooled estimate provides a consolidated view of the existing research on this topic. Moreover, we also calculated the prediction interval, which is particularly useful for estimating the range within which studies in future on this subject are likely to occur. This prediction interval was found between 2.49% and 55.90%. This wide range reflects the variability and uncertainty inherent in future research findings and is visually represented in **Figure 2**.

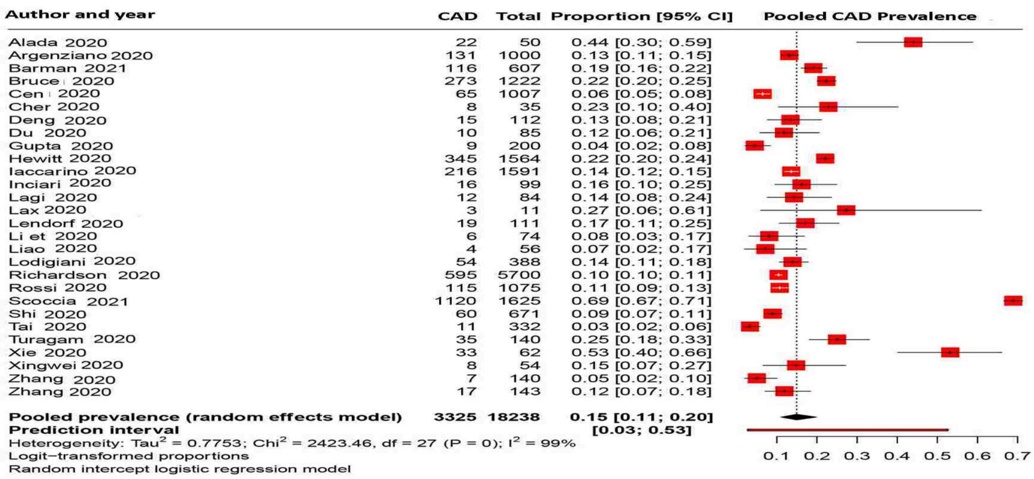

Figure 2: Meta-analysis of the prevalence of CAD in individuals with COVID-19.

Heterogeneity estimation and exploration

Estimates from each study within our meta-analysis displayed significant heterogeneity, as indicated by tau-squared value of 0.89 and I^2 of 98.9% (95% CI: 98.7% to 99.0%). Additionally, Cochran's Q test further confirmed this heterogeneity with a significant value of 4192.02 (P<.001), as determined by Wald's test. Given this high degree of heterogeneity, we opted conduct the meta-analysis with a random effect model.

To address and potentially mitigate the observed heterogeneity among these studies, we carried out subgroup analysis and meta-regression. Our subgroup analysis, utilizing geographical location, was effective in lessening heterogeneity. Studies were divided into three groups according

To their location on different continents. As indicated in the results of the test for moderators, this classification highlighted notable differences in CAD prevalence across continents (Q = 14.77, df = 3, P=0.002). The highest CAD prevalence among COVID-19 patients was observed in Europe [21.70% (14.80% - 30.65%)], while Asia had the lowest prevalence [10.07% (6.55% - 15.19%)]. This method of categorization not only clarified the variability among continents but also decreased the heterogeneity within each subgroup. Comprehensive results and analysis of these subgroup categorizations are detailed in **Table S6.**

In our effort to further explore factors influencing the heterogeneity of our meta-analysis. We conducted a meta-regression considering the sample size of each study included in the analysis. However, the results of this meta-regression didn't reveal any significant relationship between the sample size and the prevalence of CAD among COVID-19 infected individuals (P=0.11). To effectively illustrate these findings, we created a bubble plot, which is included as **Figure 3.**

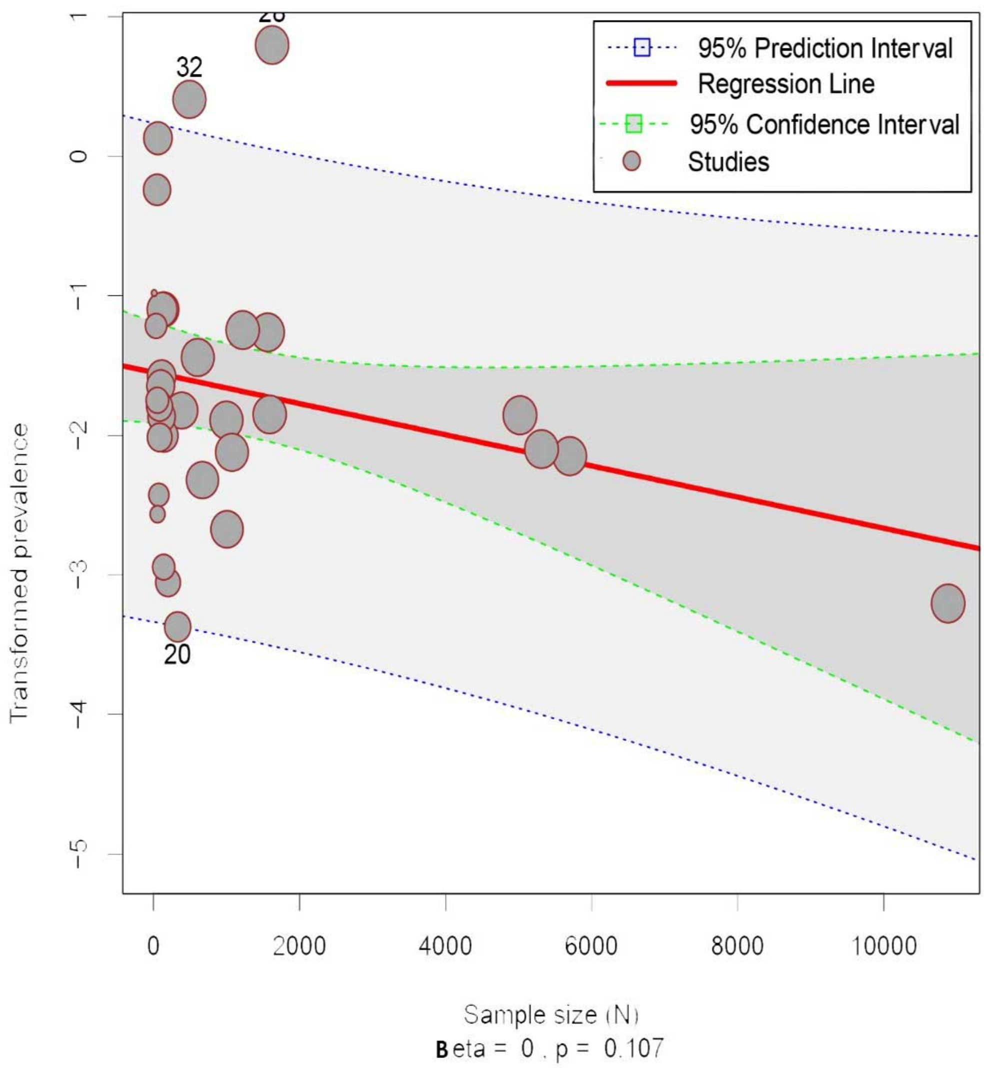

Figure 3: Bubble Plot Illustrating the association of sample size with Prevalence of CAD in COVID-19 Patients.

Publication bias assessment

To evaluate the small study effect and publication bias in our meta-analysis, we employed a Doi plot with LFK index. The Doi plot (**Figure 4**) visually represents individual study estimates, and the LFK index was calculated to be 0.57. This value indicates no significant publication bias in estimating the prevalence of CAD among COVID-19 patients.

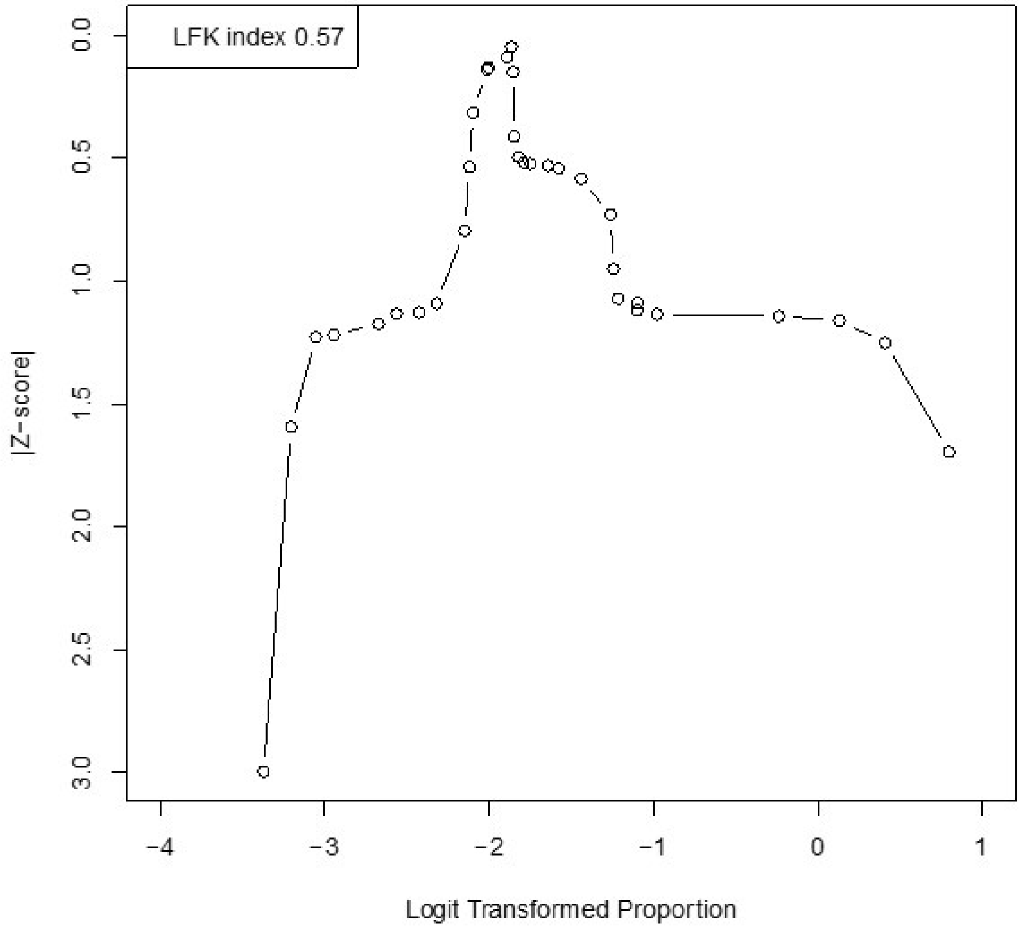

Figure 4: Publication bias assessment with Doi plot

Quality assessment

The quality appraisal of the included studies in our meta-analysis was performed with the detailed findings presented in the supplementary file (**Table S2**). The majority of these studies were regarded as having fair quality. Specifically, 32 out of the 33 studies were categorized as fair, while only one study was deemed to be of poor quality. Upon excluding the study by Barman et al [7], noted for its lower quality, there was a marginal decrease in the combined prevalence of CAD among COVID-19 patients. Omitting this study resulted in the overall prevalence changing 14.77% (95% CI: 10.84% - 19.81%) from 15.24% (95% CI: 11.41% - 20.06%), as illustrated in **Figure S1**. This adjustment showcases the impact of study quality on the overall findings of our meta-analysis.

Discussion

The findings of our analysis suggest a significant prevalence of CAD in individuals with COVID-19. The computed pooled prevalence stands at 15.24% (95% CI: 11.41% - 20.06%), with noticeable variations based on geographic location. In Europe, the prevalence is notably higher at 21.70% (95% CI: 14.80% - 30.65%), while in Asia, it's comparatively lower at 10.07% (6.55% - 15.19%). Given the extensive global impact of COVID-19, with the WHO reporting over 769 million cases by August 2023 [2], the 15.24% pooled prevalence of CAD is particularly significant. Extrapolating from this data implies that a considerable number of these COVID-19 patients might also be suffering from CAD. This underscores the critical need for a deeper understanding of this co-morbidity to enhance clinical management and potentially improve outcomes for this patient population.

The studies included in our meta-analysis exhibit considerable heterogeneity, especially in the prevalence of CAD among COVID-19 patients across different continents. This significant variation, with Europe showing the highest prevalence and Asia the lowest, could be influenced by a variety of factors. These factors include disparities in healthcare infrastructure, the capacity and accuracy of diagnostic methods, genetic predispositions among populations, lifestyle differences, and the presence of other co-morbid conditions [54]. For example, the higher prevalence of CAD in COVID-19 patients in Europe could be partially explained by its demographic composition, particularly its aging population, which is generally more prone to cardiovascular diseases [55]. This demographic aspect, coupled with other region-specific factors such as lifestyle and healthcare practices, could contribute to the higher rates of CAD observed in European individuals with COVID-19. Such observations highlight the need of considering regional and demographic variations when analyzing and interpreting health data, particularly in the context of a global pandemic.

The relationship between COVID-19 and cardiovascular complications is well-documented and recognized in the medical community. Prior research has shown that COVID-19 can aggravate pre-existing cardiovascular conditions and may also trigger new cardiac complications [56]. The virus's propensity to cause a hyperinflammatory state, along with its direct and indirect impacts on the cardiovascular system, can result in a range of issues including myocardial injury, arrhythmias, and thromboembolic events. This is of particular concern for patients with existing CAD. Supporting this, a study from China found that myocardial injury among individuals infected with COVID-19 markedly raises the risk of mortality [57]. This underscores the critical importance of monitoring and managing cardiovascular health in patients affected by COVID-19, especially those with pre-existing CAD.

In a cohort study conducted across three hospitals in Wuhan, 1007 patients with mild to moderate COVID-19 were examined, researchers focused on identifying risk factors that contribute to disease progression. During a follow-up period of 28 days, it was observed that 71.50% of the patients either remained stable or showed signs of recovery. However, 22.05% of the patients progressed to severe illness, 2.18% became critically ill, and 4.27% succumbed to the disease.

The study identified several factors that were significantly associated with the progression of COVID-19. These included being over the age of 65, male gender, and having pre-existing health conditions like hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and CAD. Notably, the presence of CAD emerged as a considerable risk factor for the progression of COVID-19, with a hazard ratio (HR) of 1.83 (95% CI: 1.26–2.66))[25]. This finding highlights the importance of closely monitoring and managing patients with CAD who contract COVID-19, given their increased risk of developing more severe symptoms and complications.

Research has consistently linked cardiovascular diseases like coronary heart disease to a heightened risk of severe COVID-19 and increased mortality rates. Therefore, understanding the prevalence of coronary heart disease is crucial for effectively allocating resources in cardiovascular healthcare [41]. Our study gathers data from various global locations, offering insights into the diverse complications of the disease [31]. In a Chinese study involving 332 COVID-19 patients, 23 out of 48 patients with cardiovascular issues experienced severe symptoms necessitating immediate ICU care [47]. Another investigation found that COVID-19 patients with cardiac injuries also had a higher occurrence of acute respiratory distress [7]. In a different study of 62 patients, where 33 had cardiovascular diseases, 3.2% experienced severe infection and required ventilator support [49]. Contrastingly, some research indicates a reciprocal relationship between COVID-19 and cardiovascular events like stroke. For instance, in the Philippines, a study of 10,881 COVID-19 patients identified a 3.4% stroke incidence, leading to more ICU admissions and deaths [33]. Additionally, previous studies have suggested that SARS-CoV-2 can invade cardiac cells, potentially causing conditions like myocardial inflammation and CAD [58].

Raising awareness about the necessity of regular cardiac screenings for COVID-19 patients is vital. Early identification of CAD can facilitate prompt medical interventions, thereby improving the management and treatment outcomes for these patients. This approach becomes especially important considering the heightened complications observed in COVID-19 patients with pre-existing cardiovascular conditions, including a greater need for ICU care and more complex recovery processes [56].

In the context of the evolving COVID-19 pandemic, it is crucial for healthcare professionals to remain alert to the potential cardiovascular complications in patients with COVID-19. There is a pressing need for more in-depth research to explore the mechanisms underlying of the link between COVID-19 and cardiovascular issues, then to devise strategies to reduce associated risks. Future studies should focus on a broader range of cardiovascular diseases, including myocardial infarction, atherosclerosis, thrombosis, heart failure, and stroke, potentially through subgroup analyses of these specific complications. While this study has specifically concentrated on CAD, it opens avenues for further investigation into other cardiovascular conditions in a similar or different context. Such research would empower researchers, healthcare workers and policymakers to more effectively evaluate and address the challenges in this domain. This meta-analysis, which effectively summarizes the prevalence of CAD among COVID-19 patients and examines the associated heterogeneity, was conducted with thorough methods, including a robust assessment for publication bias. Although no evidence of small-study effects was detected, it's important to acknowledge certain limitations. The substantial heterogeneity observed, albeit somewhat mitigated through subgroup analysis, indicates that the characteristics of individual studies may affect the reported prevalence rates. Furthermore, the quality assessment of the studies suggests that while most were of fair quality, one was deemed of poor quality, underscoring the necessity for more high-quality research to further clarify the relationship between CAD and COVID-19.

Conclusions

Our analysis encompassed 40,064 individuals across 33 studies, revealing that 5,333 of these were COVID-19 patients also diagnosed with CAD. This showed a combined prevalence of 15.24 % for CAD in patients with COVID-19. Owing to the significant prevalence, it's imperative to routinely monitor the cardiac health of COVID-19 patients who are hospitalized. The observed association between these two conditions has substantial implications for patient management and outcomes, highlighting the need for heightened vigilance and targeted care strategies for this patient group.

Supporting information

Download: Supplementary Table S1, S2, S3, S4, S5 and S6 | Figure S1

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). **Behdin Nowrouzi-Kia**: Conceptualization (supporting); Writing – original draft (supporting); Writing – review and editing (equal). **Vijay Kumar Chattu**: Conceptualization (supporting); Writing – original draft (supporting); Writing – review and editing (equal). **Sanghamitra Pati**: Conceptualization (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal).

All authors attest they meet the ICMJE criteria for authorship and gave final approvalforsubmission.

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 declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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