Systematic Review

Association between Influenza and COVID-19 Viruses and the Risk of Atherosclerosis: Meta-Analysis Study and Systematic Review

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Highlights:
- Atherosclerosis is an important issue in health care systems and one of the main causes of morbidity and mortality in patients.
- There is evidence of an association between infectious diseases and atherosclerosis.
- The present study demonstrates that infections with influenza and COVID-19 are risk factors for atherosclerosis.
- It seems necessary to consider different strategies for managing and eradicating viral infections.

Abstract: There is a lot of evidence to suggest that patients infected with the COVID-19 and influenza viruses are at risk of atherosclerosis. Additionally, there are heterogeneous studies on the risk of atherosclerosis in patients infected with the influenza and COVID-19 viruses. We conducted a case-control and cross-sectional study and examined the association between the risk of atherosclerosis, and influenza virus (IV-A and IV-B) and COVID-19 infections in this study. We searched for keywords such as influenza virus, COVID-19 and atherosclerosis in English and Persian in well-known databases such as PubMed, SID, Magiran and Google Scholar. In this study, we analyzed the information using a meta-analysis, the random effect model, the I2 index and STAT (version 11.2). The results from the analysis of ten studies on influenza virus and nine studies on COVID-19 reviewed individually (totaling 6428 samples for influenza virus infections and 10,785 samples for COVID-19 infections) demonstrated a risk of atherosclerosis in patients with influenza and COVID-19 infections, with an OR (odds ratio) = 0.45 ((95% CI): 0.25 to 0.64) and an OR (odds ratio) = 1.04 ((95% CI): 0.82 to 1.26), respectively. The present study provides new insights into the risk of atherosclerosis in patients infected with the COVID-19 and influenza viruses. Therefore, it seems necessary to consider different strategies for managing and eradicating viral infections among individuals.

Keywords: influenza virus; COVID-19; SARS-CoV-2; 2019-nCOV; atherosclerosis; meta-analysis

1. Introduction

Preventive health care has been proposed to reduce the heavy burden of health care in communities worldwide [1]. Atherosclerosis is one of the leading causes of morbidity and mortality in older adults in developed countries [2]. Furthermore, many efforts have been made to correct or treat atherosclerosis and its complications. Additionally, atherosclerosis, as an inflammatory disease, affects the walls of blood vessels. This disease is characterized by the accumulation and progression of lipids in the walls of the arteries [3]. Furthermore,
many factors cause atherosclerosis, including smoking, high blood pressure, many diseases and other environmental factors [4].

Many seroepidemiological studies have shown that persistent infections with bacterial or viral agents may be associated with atherosclerosis [5]. Evidence suggests that human atherosclerosis is associated with previous exposure to some pathogens such as Chlamydia pneumoniae, Helicobacter pylori, HIV, Porphyromonas gingivalis, CMV, Herpes simplex virus types 1 and 2, Entro viruses, hepatitis A and influenza virus [6].

In a recent outbreak of COVID-19 infections, significant mortality was attributed to heart disease and atherosclerosis [7]. Previous studies have demonstrated conflicting reports on the association between infections with the influenza virus (IV) and coronavirus, and artherosclerosis [8]. The results of some studies have demonstrated that influenza virus (IV-A and IV-B) and COVID-19 infections cannot predict the risk of artherosclerosis and that the infectious burdens of these diseases are independent [9]. On the other hand, some researchers suggested that influenza virus (IV-A and IV-B) and COVID-19 infections may play roles in the development of atherosclerosis by specific mechanisms [10].

Due to the recent influenza virus (IV-A and IV-B) and COVID-19 epidemics, and the acute condition of patients with atherosclerosis, we hypothesized that previous COVID-19 and influenza virus (IV-A and IV-B) infections were associated with atherosclerosis. To prove this hypothesis, we conducted a meta-analysis study and systematic review study to investigate the association between influenza virus (IV-A and IV-B) and COVID-19 infections, and atherosclerosis.

2. Methods

2.1. Study Instructions

The present study was conducted according to the PRISMA guidelines [11]. The study steps included searching for articles, selecting articles, evaluating the quality of the studies, extracting article information and performing statistical analyses. All steps were performed independently by two different authors. The third author supervised the collection of studies and acted as a judge for disagreements.

2.2. Eligibility Criteria and Information Sources

In order to identify appropriate studies on the risk of atherosclerosis in patients with COVID-19 and influenza, we considered case–control and cross-sectional studies. In this study, to avoid bias, all steps in the collection of studies were performed by two researchers. The third researcher only stepped in to further monitor and manage the process.

2.3. Search Strategy

We searched well-known databases. At first, reputable databases containing medical information were searched until 16 August 2020. These databases included ISI, Pubmed, EMBASE, MEDLINE, Cochrane and Google scholar. In this study, the search was performed based on the following keywords: “influenza virus” [MeSH], “coronavirus” [MeSH], “COVID-19” [MeSH] and “atherosclerosis”.

2.4. Quality of Evaluation

In the present study, the Newcastle–Ottawa Scale (NOS) was used to evaluate non-standard studies. Finally, according to this checklist, the two researchers rated each of studies. To evaluate the quality, “high”, “medium” or “low” quality were considered for the articles. Hence, for each study, a score of more than 7 was considered to be of “high quality”, a score of 4–6 was considered to be of “average quality”, and a score of less than 4 was considered to be of “low quality”.
2.5. Included and Excluded Studies

In the present study, the inclusion criteria for CC studies (case–control studies) and CS study (cross-sectional studies) included influenza and coronavirus infections in patients with atherosclerosis.

The exclusion criteria include (1) studies that did not focus on influenza and coronavirus infections in patients with atherosclerosis, (2) duplicate studies, (3) studies with the full text not written in English, (4) studies for which the full text was inaccessible, and (5) studies that were not relevant to this topic.

2.6. Study Selection

In this study, all studies were imported into Zotero software (5.0.21; GMU, CHNM, Fairfax, VA, USA), and duplicate studies were eventually removed after “Finding Updates”. After deleting the authors names, journal names, and year of publication for all studies, each study was evaluated independently by the authors. In this study, all articles were screened separately by two authors (articles were reviewed by reading the title and summary of the article, as well as the titles and criteria for entry and exit of all articles (eligibility stage)). An expert researcher also participated in the final selection of articles, and the final decision was made by the expert researcher.

2.7. Information Extraction

In summary, an appropriate checklist was considered for the present study. The checklist included the author name(s), year of publication, place of study, sample size, tracking time, relative risk (RR), odds ratio (OR) with 95% CI (confidence interval), number of events in both groups (case and control) and age of participants. Additionally, the data were extracted by two researchers separately. The third researcher managed and monitored the information.

2.8. Statistical Analysis

In the present study, two tests were used to evaluate the articles: these two tests included Cochran’s Q test and the I² index. The I² index consists of four categories. A description of the classification of this index is described in Reference [12]. To obtain heterogeneity in articles, the subgroup analysis method was used. To measure the predictive power of each article, the sensitivity analysis method was used. To measure publication bias in the articles, Funnel design tests, and Egger and Begg tests were used. Finally, to obtain the statistical results, Version 2 of the meta-analysis software including: meta version 4.9-1 with R software version 3.5.1 was used. A value of \( p < 0.05 \) was considered for the evaluation of the tests.

3. Results

3.1. Search for Studies

A total of \( N = 287 \) studies were obtained from well-known databases and evaluated by two authors; the authors manually identified \( N = 21 \) articles (a total of 240 articles on influenza viruses and 68 articles on COVID-19 infection), and \( N = 199 \) (143 articles on influenza viruses and 56 articles on COVID-19 infection) articles were ruled out due to duplication. After screening the title and abstracts, \( N = 155 \) (110 articles on influenza viruses and 45 articles on COVID-19 infection) articles were ruled out due to irrelevancy. After finding the full text of an article, \( N = 102 \) (68 articles on influenza viruses and 34 articles on COVID-19 infection) articles were removed because their focus was not on our topic of interest. Additionally, articles with the full text not written in English or with inaccessible full texts (\( N = 37 \) (19 articles on influenza viruses and 18 articles on COVID-19 infection), letters to the editor without original information and true data (\( N = 12 \) (6 articles on influenza viruses and 6 articles on COVID-19 infection), review articles and case reports (\( N = 39 \) (25 articles on influenza viruses and 3 articles on COVID-19 infection), and articles of a low quality (\( N = 7 \) (14 articles on influenza viruses and 4 articles on COVID-19 infection).
infection) were removed. Finally, \( N = 19 \) (10 articles on influenza viruses and 9 articles on COVID-19 infection) articles of good quality were included in this study (Figure 1).

Figure 1. Flowchart of the selection studies for the analysis of influenza virus and its association with atherosclerosis (A). Flowchart of the selection studies for the analysis of COVID-19 (coronavirus) and its association with atherosclerosis (B).
3.2. Article Exclusivities

Relevant articles about atherosclerosis published in English were considered per the inclusion criteria. Articles with a selected non-random sample size, articles not related to the topic of interest, letters to the editor and case reports were removed (as explained in more detail above).

3.3. Risk of Bias in Articles

In the present study, articles of all methodological types were reviewed and then selected. Additionally, papers were evaluated according to their method and needed to receive sufficient points before inclusion in the present study.

3.4. Outcome of Articles

In an initial search performed by two independent researchers, the present study searched for related articles ($N = 287$) in the various databases mentioned above. The final articles consisted of CC studies (case–control studies) and CS studies (cross-sectional studies) that individuals met the criteria for entering meta-analysis and systematic review (Figure 1A,B).

3.5. Evaluation of Outcome

From a statistical point of view, an estimation of the association between influenza virus and COVID-19 (coronavirus) infections, and atherosclerosis is critical, and in the present study, we obtained OR (odds ratio) = 0.45 (95%CI: 0.25 to 0.64) and OR (odds ratio) = 1.04 (95%CI: 0.82 to 1.26), respectively (Figure 2).

![Figure 2](A)

Figure 2. Cont.
3.6. Additional Outcome

In the present study, a qualitative evaluation was performed. A quality rating was given to these studies (Tables 1 and 2). In the present study, articles on the relationship between influenza virus infection and atherosclerosis were separated for different types of influenza virus (types IV-A and IV-B) in separate flowcharts (Figure 3). Additionally, in another flowchart, the relationship between coronavirus infection and atherosclerosis was separated based on the months of the year 2020 (Figure 4).
Table 1. Characteristics of the studies included in the meta-analysis study on the association between influenza virus and atherosclerosis.

| ID | Ref | Writer | The Year the Study Was Conducted | The Country in Which the Study Was Conducted | Design | The Average Age of Study Participants | Effective Size OR | 95% CI | p Value | Number of Sample | Type of Flu | Quality |
|----|-----|--------|----------------------------------|---------------------------------------------|--------|--------------------------------------|------------------|--------|----------|----------------|-------------|---------|
| 1  | [13]| Chiang| 2017 Taiwan                       | CC                                          |        | 76.8                                 | 0.8              | 0.78   | 0.82     | 0.01           | 160         | IV-B    | High    |
| 2-1| [14]| Guan  | 2008 China                        | CC                                          |        | 60.0                                 | 3.3              | 1.5    | 7.04     | 0.003          | 209         | IV-A    | Moderate |
| 2-2| [14]| Guan  | 2008 China                        | CC                                          |        | 60.0                                 | 7.5              | 1.3    | 43.0     | 0.001          | 209         | IV-B    | Moderate |
| 3-1| [15]| Xiuru Gu| 2012 China                      | CC                                          |        | 57.0                                 | 3.1              | 1.5    | 6.4      | 0.004          | 252         | IV-A    | High    |
| 3-2| [15]| Xiuru Gu| 2012 China                      | CC                                          |        | 57.0                                 | 10.2             | 5.7    | 20.0     | 0.001          | 252         | IV-B    | High    |
| 4  | [16]| Barbera| 2016 Spain                       | CS                                          |        | 85.0                                 | 1.64             | 1.33   | 2.02     | 0.001          | 728         | IV-A    | Moderate |
| 5  | [17]| Mohammad| 2020 Sweden                      | CS                                          |        | 75.0                                 | 1.05             | 1.02   | 1.08     | 0.002          | 562         | IV-A    | Moderate |
| 6-1| [18]| MacIntyr| 2013 Australi                    | CC                                          |        | 65.0                                 | 0.55             | 0.35   | 0.85     | 0.008          | 559         | IV-B    | Weak    |
| 6-2| [18]| MacIntyr| 2013 Australi                    | CC                                          |        | 65.0                                 | 1.98             | 1.2    | 3.3      | 0.001          | 559         | IV-A    | Weak    |
| 7  | [27]| Clayton| 2005 USA                         | PHS                                         |        | 63.0                                 | 1.0              | 0.5    | 1.9      | 0.002          | 534         | IV-A    | High    |
| 8  | [19]| Gash  | 2013 London                       | CC                                          |        | 40.0                                 | 3.17             | 0.61   | 16.47    | 0.002          | 137         | IV-B    | High    |
| 9  | [20]| Penttine| 1996 Finland                     | CC                                          |        | 49.5                                 | 1.77             | 1.07   | 2.93     | 0.001          | 3172        | IV-A    | Moderate |
| 10 | [21]| Clayton| 2007 UK                          | CC                                          |        | 72.0                                 | 2.48             | 1.67   | 3.7      | 0.002          | 115         | IV-A    | Moderate |

N total: 6428

OR: odds ratio, CC: case–control studies, CS: cross-sectional study, N and NO: number, PHS: prospective hospital-based study.

Table 2. Characteristics of the studies included in the meta-analysis study on the association between COVID-19 (coronavirus) infection and atherosclerosis.

| ID | Ref | Author   | Years | Months | Country | Design | Mean Age | Effect Size | p Value | Sample Size | Quality |
|----|-----|----------|-------|--------|---------|--------|----------|-------------|---------|--------------|---------|
| 1  | [22]| Mandeep  | 2020  | May    | Boston  | CS     | 65       | 2.70        | 2.08    | 3.51         | 0.001   | 8910     | Moderate |
| 2  | [23]| Shi Tai  | 2020  | August | China   | CC     | 51       | 2.65        | 1.01    | 6.89         | 0.001   | 332      | High     |
| 3  | [24]| Yun Feng | 2020  | April  | China   | CC     | 58       | 3.02        | 1.45    | 6.32         | 0.004   | 476      | High     |
| 4  | [25]| Huang    | 2020  | February | China   | CC     | 49       | 2.05        | 0.43    | 14.54        | 0.001   | 41       | Moderate |
| 5  | [7] | Qin      | 2020  | April  | China   | CC     | 61       | 4.98        | 1.48    | 16.79        | 0.002   | 452      | Weak     |
| 6  | [8] | Wan      | 2020  | March  | China   | CC     | 56       | 16.59       | 1.93    | 142.0        | 0.002   | 135      | Moderate |
| 7  | [9] | Wang     | 2020  | February | China   | CC     | 66       | 2.76        | 1.03    | 7.35         | 0.001   | 138      | High     |
| 8  | [10]| J. Zhang | 2020  | February | China   | CC     | 64       | 1.95        | 0.62    | 34.11        | 0.004   | 140      | High     |
| 9  | [26]| F. Zheng | 2020  | January | China   | CC     | 57       | 4.61        | 0.62    | 34.11        | 0.002   | 161      | Moderate |

N total: 10,785

OR: odds ratio, CC: case–control studies, CS: cross-sectional study, N and NO: number.
Figure 3. A meta-analysis of the relationship between influenza virus types (types A and B) and atherosclerosis was performed. Throughout this chart, the studies are separated based on the types of influenza virus and their associations with atherosclerosis, supported by a random effects model; [13–21]. PRISMA model in meta-analysis studies [11].

| Study ID | ES (95% CI) | Weight |
|----------|-------------|---------|
| IV-B     |             |         |
| Chiang (2017) | -0.22 (-0.25, -0.20) | 15.52   |
| Guan (2008)  | 2.01 (0.27, 3.76)   | 1.12    |
| Xiuru Gu (2012) | 3.23 (1.69, 2.95)  | 5.86    |
| Gash (2013) | 1.15 (-0.49, 2.80) | 1.25    |
| Subtotal (I-squared = 95.8%, p = 0.000) | 1.27 (-0.47, 3.01) | 23.76   |
| IV-A     |             |         |
| Guan (2008)  | 1.19 (0.42, 1.97)   | 4.43    |
| Xiuru Gu (2012) | 1.13 (0.41, 1.86)  | 4.85    |
| Barbera (2016) | 0.49 (0.29, 0.70)  | 13.15   |
| Mohammad (2020) | 0.05 (0.02, 0.08)  | 15.51   |
| MacIntyr (2013) | -0.60 (-1.04, -0.15) | 8.52    |
| Clayton (2005) | 0.00 (-0.67, 0.67) | 5.42    |
| MacIntyr (2013) | 0.68 (0.18, 1.19)  | 7.50    |
| Penttine (1996) | 0.57 (0.07, 1.07)  | 7.53    |
| Clayton (2007) | 0.91 (0.51, 1.31)  | 9.35    |
| Subtotal (I-squared = 88.5%, p = 0.000) | 0.44 (0.13, 0.76) | 76.24   |
| Overall (I-squared = 96.7%, p = 0.000) | 0.45 (0.25, 0.64) | 100.00  |

NOTE: Weights are from random effects analysis.
Figure 4. The correlation between a coronavirus or COVID-19 infection and atherosclerosis was assessed. Throughout this chart, the studies are separated based on the months of 2020, supported by a random effects model conducted by various authors; [8–10,22–26]. PRISMA model in meta-analysis studies [11].

4. Discussion

Consolidation of Evidence

Today, infectious diseases affect people much more severely and are spreading at a higher rate in all parts of the world. In the United States and most other developed countries, atherosclerosis is one of the leading causes of morbidity and mortality. In 2016, atherosclerosis, which affects the arteries of the heart and brain, caused nearly 18 million deaths worldwide. Atherosclerosis, or hardening of the arteries, is a complication that causes plaque to form inside the arteries [28,29]. Plaques are made of cholesterol, fatty substances, cell waste products, calcium and fibrin (blood-clotting agent) [30]. There is evidence of an association between infectious diseases and atherosclerosis. There are studies that have suggested bacterial and viral pathogens as one of the initiators or enhancers of atherosclerosis [31]. Several seroepidemiological and immunohistochemical studies were
performed on viral infections, especially on different types of influenza viruses and on the novel coronavirus (COVID-19), with atherosclerosis [22]. Several studies demonstrated a possible association between influenza virus and coronavirus infections as a risk factor for plaque rupture (thrombosis) and infarction [23]. On the other hand, the effects of influenza virus and COVID-19 infections on atherosclerosis are highly controversial [24]. According to these confusing results, we decided to investigate the roles of influenza viruses (IV-A and IV-B) and coronavirus in atherosclerosis in the form of a meta-analysis study. Finally, in the present article, different types of influenza virus (IV-A, IV-B) and coronavirus were considered as two emerging risk factors in atherosclerosis.

5. Conclusions

In the present article, the association among influenza virus, COVID-19 (coronavirus), and atherosclerosis was evaluated. Briefly, from the results of this study, there is a relationship between the presence of influenza virus and coronavirus infections, and atherosclerosis. In addition, the results of this study showed that infections with the influenza virus and the coronavirus are one of the risk factors for atherosclerosis [25]. Therefore, a new approach must be taken to manage viral infections.

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