

Co-infection of SARS-CoV-2 with influenza among COVID-19 cases: A-meta analysis

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Systematic Review

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Abstract

Background The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that causes coronavirus disease 2019 (COVID-19) is a public health problem and may have co-infection with other pathogens such as influenza virus.

Objective This study aims to assess the co-infection of SARS-CoV-2 with influenza among COVID-19 cases.

Material and methods The all relevant studies were collected from international databases. For improving the quality of the present literature, the all studies were evaluated by two reviewers in order to confirm all of the studies have inclusion criteria. Finally, all articles with sufficient quality scores were included in meta-analysis. Assessment of heterogeneity among the studies of primary studies was performed using the statistic chi-squared test (Cochran's Q) and I^2 index. In this results, random or fixed effect model were used for determination of heterogeneity test. All statistical analyses were performed using Comprehensive Meta-Analysis (CMA), V.2 software.

Results This meta- analysis included 9 primary studies investigating the co-infection of SARS-CoV-2 with influenza among COVID-19 cases. Pooled prevalence (95% confidence interval) of co-infection is shown that the prevalence of influenza A is higher than influenza B. 2.3(0.5-9.3) vs 0.1 (0.4-3.3). Using the fixed effect model the frequency of fever was (80.6% [95% CI 76.1–84.40, $p < 0.153$]) and it is shown that fever is the most prevalent symptom in patients.

Conclusion Patients admitted to hospital with COVID-19 also infected with influenza virus. Thus, the current research provides a better understanding about the control and treatment of co-infection with SARS-CoV-2 and the influenza virus.

Introduction

Coronavirus is a family of RNA viruses that can cause of common cold, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) with the mortality rate of 10% and 37%, respectively (1). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, that causes coronavirus disease 2019 (COVID-19) was discovered in Wuhan, China and expanded in all over the world from 31 December and spread across the continents (2, 3). The earliest countries (China, South Korea, and Iran) announced the COVID-19 outbreak as a public health problem(4).

The coronavirus's 3000 nucleotide genome encodes four structural protein such as, Spike (S) protein, Nucleocapsid (N) protein, Membrane (M) protein, envelop (E) protein and several non-structural proteins (nsp) (5). Spike (S) protein consist of transmembrane (TM) domain which is able to bind a host receptor. Nuclear capsid or N-protein which is bound to the virus single positive strand RNA, is located inside in the capsid. Nucleoprotein gene plays key role in virus's replication and transcription; it allows the virus to hijack human cells and turn them into virus factories (6). M protein is the most abundant protein in the viral surfaces which is the central organizer for the virus protein. The E-protein is a small membrane protein, plays an important role in virus assembly subunits, membrane penetrance of the host cell and interaction between viruses and host cells (7).

The symptoms of COVID-19 can include fever, cough, sore throat, fatigue, shortness of breath and gastrointestinal symptoms such as diarrhea and nausea (8, 9). Coronaviruses have been responsible for the common cold by a long time and it is reported that the symptoms of SARS-CoV-2 disease in human is similar to the common cold or influenza; but the infection and mortality rate of the SARS-CoV-2 is higher than other respiratory infections. SARS-CoV-2 is a contiguous virus and can be transmit by the infected person breathed, coughed, or sneezed (10). Study shows that SARS-CoV-2 may have co-infection with other pathogens such as viruses, bacteria, and fungi which are related to increase in hospitalization rate and mortality. It is reported that the most co-infection occur with influenza virus (11). Influenza is a respiratory illness with the sign of fever, chills, body aches, sore throats, nasal congestion, fatigue, vomiting, abdominal pain, and diarrhea, and seems to have similar transmission character with COVID-19 (12, 13). Recently study have clarified that there are Immunopathological similarities between influenza and SARS-CoV-2 (14). Several studies from United Sate of America (15, 16), china (17) and Iran (18) show that there is co-infection with SARS-CoV-2 and influenza A and B virus. In addition some researches indicate that the co-infection of SARS-CoV-2 with influenza in patients suffering from pneumonia, sinus infection, bronchitis and cardiovascular disease (CVD) promote the mortality rate (18-20).

Researchers found that patients admitted to hospital with COVID-19 also infected with influenza virus. Thus, the current research provides a better understanding about the control and treatment of co-infection with SARS-CoV-2 and the influenza virus. So, This study aims to assess the co-infection of SARS-CoV-2 with influenza among COVID-19 cases.

Material And Methods

Search strategy

The all published studies were searched using ISI, Science direct, Scopus, Pubmed, Google scholar, and Wiley online international databases from December 2019 to January 2020. The search strategy was done using the following key words: "co-infection", "COVID-19 virus", "Influenza", "influenza virus", "Human flu", "SARS-CoV-2", "severe acute respiratory syndrome coronavirus 2", "coronavirus disease 2019 virus", "2019 novel coronavirus". AND/'OR' operators were used to identify the articles. For improving the quality of the present literature, the references of studies were examined. In addition, all titles and abstracts were randomly evaluated by two reviewers in order to confirmed all of the studies have inclusion criteria and their results were compared with each other.

Inclusion/exclusion criteria

All articles with sufficient quality scores were included in meta-analysis following inclusion criteria: 1) All English studies. 2) Patients with confirmed diagnosis of COVID-19. 3) Studies based on prevalence of influenza among COVID -19 patients. 4) Reported prevalence of clinical characterization among co-infected patients. 5) Result of abnormalities in chest among co-infected patients.

The excluded studies were as follows: 1) Articles with no access to the full-text. 2) Case reports or case series studies. 3) Duplicated studies. 4) Studies published in languages other than English. 5) Abstracts, cases, and review studies. 6) Studies that did not report data on co-infection.

Quality assessment

At first, after identification and screening of studies, articles were assessed for eligibility, and finally suitable studies were included to the Meta-analysis review. In the present study, The STROBE checklist was used for evaluation of the quality of the selected articles based on title and contents. The STROBE checklist composed of 22 items covering all of the aspects of the methodology such as collection methods, tools, type of the study, definition of the variables, statistical analysis tests, study objectives, sample size and study population.

Depending on the quality analysis, each question was assigned to score one point. In this checklist, the final scores for each study could range from 0 to 44, respectively. Based on the results of the quality assessment, studies were divided into three categories: Low (<15.5), average (15.5–29.5) and high quality (>30) and studies with low-quality scores were excluded from the final meta-analysis.

Data extraction

The following variables were extracted from the appropriate articles: first author, publication date, type of study, geographical regions, study language, number of SARS-CoV-2 confirmed patients, total influenza, influenza A, influenza B, co-infected patients with clinical characterization (fever, cough, fatigue, diarrhea, difficult breathing), radiological data (Chest CT). The information preparation was done in Microsoft excel spreadsheet and all statistical analyses were carried out via Comprehensive Meta Analysis V.2 software.

Statistical analysis

In our research, the primary outcome was the prevalence of influenza in COVID-19 patients and the secondary outcome was the prevalence of clinical characterization in co-infected patients. Assessment of heterogeneity among the studies of primary studies was performed using the statistic chi-squared test (Cochran's Q) and I^2 index. In this results, random or fixed effect model were used for determination of heterogeneity test and more than 50% were considered as the degree of heterogeneity. For study heterogeneity evaluation, a forest plot estimated with confidence intervals of 95%. (CIs; horizontal lines). All statistical analyses were performed using Comprehensive Meta-Analysis (CMA), V.2 software.

Results

A total of 1031 articles were obtained using the electronic strategy search. After removing of 78 duplicate articles, 1453 study were remained for screening. Then, the full-text of the articles was evaluated and 1289 irrelevant articles were excluded. At the eligibility check stage, 164 articles were examined and 155 of them were omitted. Finally, 9 articles were included in this meta-analysis review, according to PRISMA (Preferred reporting items for systematic review and meta-analysis) guideline. Figure 1 shows the review process for the included studies.

Accordingly, this Meta-analysis shows the estimation of the influenza prevalence among patients infected with COVID-19 (Table 1). In nine cross sectional studies, the influenza prevalence among patients infected with COVID-19 varied from 0.08 in Nowak study to 49.46% in

Simin Ma study. In the present study the clinical characterization among patients infected with COVID-19 and influenza is shown in Table 2.

Co-infection of SARS-COV-2 and influenza

Generally, with the compounding of the results, the influenza prevalence among co-infected patients with the confidence interval of 95 % and with based on random effect model is (I^2 :95.948%) and it is shown that heterogeneity was observed among the primary results of the studies (Fig 2). Significant statistical heterogeneity based on random effect model are found in the analysis of the influenza (A, B) prevalence among co-infected patients (I^2 = 95.977%), and (I^2 = 77.350) respectively. The current result is shown that the prevalence of influenza A is higher than influenza B. 2.3(0.5-9.3) vs 0.1 (0.4-3.3). (Figure 3, 4).

Prevalence of clinical characterization and chest radiography among co-infected patients

The forest plot analyses were performed for fever, chest CT abnormalities, diarrhea, fatigue, cough, and difficult breathing.

Fever analysis

Figure 5 (A) shows that most co-infected patients had fever. In the present study, the prevalence of fever is reported in 5 articles comprising 291 patients and ranged between 69.56-100%. Combination of these studies in the same manner as for fever, using the fixed effect model revealed that the frequency of fever is (80.6% [95% CI 76.1–84.40, $p < 0.153$]).

Cough analysis

A total of 5 articles including 124 patients reported on the prevalence of cough, which ranged from 24.83-100%. Due to the heterogeneity in the results of the primary studies, the random-effects model used for assessment. By combining these 6 articles, it is revealed that cough is the second most common symptom presenting in co-infected patients (43.3% [95% CI 24.1–64.8, $p = 0.000$]). Figure 5 (B).

Fatigue analysis

The prevalence of fatigue is assessed in 5 articles including 37 patients and the rate of fatigue varied between 3.26 and 40%. Based on the homogeneity between the results of the primary studies the fixed effects model was used for assessment. By revealing of articles, the frequency of fatigue in patients is (13.8% [95% CI 5.6–30.3, $p = 0.000$]). Figure 5 (C).

Diarrhea analysis

The prevalence of diarrhea is reported in 4 articles comprising 35 patients and ranged from 3.92–40% respectively. Based on the heterogeneity between the results of the primary studies, the random-effects model was used for assessment. By combining of these articles, diarrhea is determined to have a prevalence of (12.2% [95% CI 3.9–32.3, $p = 0.000$]). Figure 5 (D).

Difficult breathing analysis

Difficult breathing was less common in the patients of COVID-19 and influenza. The prevalence of difficult breathing assessed in 4 articles comprising 27 patients and is reported to range from 6.87–100%. Due to the heterogeneity in the results of the primary studies, the random-effects model was employed. Combined analysis of these articles revealed that difficult breathing occurred in (9.3% [95% CI 3.7–21.5, $p < 0.010$]). Figure 5 (E).

Chest radiography

Among the selected studies, the prevalence of CT abnormalities is reported in 5 articles comprising 272 patients and ranged from 83–100%. By combining the results of these 3 studies, the frequency of CT abnormalities in co-infected patients is (66.8% [95% CI 29.4–90.7, $p < 0.001$]). As there is heterogeneity between the results for CT abnormalities, the random-effects model was used for assessment. Figure 5 (B).

Table 1: Estimation of the influenza prevalence among patients infected with COVID-19

Influenza B	Influenza A	Total influenza	Number of SARS-CoV-2 patients	Language	Authors	Reference
N/A	N/A	19 (37.25)	51	English	Castillo (2020)	(21)
23 (7.49)	153 (49.83)	131 (42.67)	307	English	Yue(2020)	(22)
1 (0.4)	2 (0.8)	22 (8.8)	250	English	Ma(2020)	(23)
N/A	1 (0.08)	1 (0.08)	1204	English	Nowak(2020)	(24)
2 (1.73)	3 (2.60)	5 (4.34)	115	English	Ding(2020)	(25)
N/A	23 (21.90)	49 (46.66)	105	English	Hashemi1 (2020)	(26)
N/A	N/A	46 (49.46)	93	English	Simin Ma(2020)	(27)
5 (1.94)	2 (0.77)	34 (13.22)	257	English	Zhua(2020)	(28)
0	N/A	1 (4.16)	24	English	YanJun(2020)	(29)

Table 2: Estimation of clinical characterization among patients infected with COVID-19 and influenza.

Chest CT, Abnormalities	Difficult breathing	Diarrhea	Fatigue	Cough	Fever	Number of patients	Area	Language	Authors	Reference
122 (93.12)	9 (6.87)	11 (8.39)	13 (9.92)	40 (30.53)	104 (79.38)	131	Wuhan	English	Yue(2020)	(22)
127 (83)	11 (7.18)	6 (3.92)	5 (3.26)	38 (24.83)	132 (86.27)	153	Wuhan	English	Yue(2020)	(22)
23 (100)	2 (8.69)	0 (0)	3 (13.04)	6 (26.08)	16 (69.56)	23	Wuhan	English	Yue(2020)	(22)
N/A	5 (100)	2 (40)	2 (40)	5 (100)	5 (100)	5	China	English	Ding(2020)	(25)
N/A	N/A	16 (34.78)	14 (30.43)	35 (76.08)	34 (73.91)	46	China	English	Simin Ma(2020)	(27)
272	27	35	37	124	291	358	Total of samples			

Discussion

SARS-CoV-2 and influenza infection are associated with respiratory disorders, and signs in patients can vary from moderate to severe morbidity and mortality (30). Some studies and case reports indicate that influenza co-infection with COVID-19 may be important for the infected patient's severity (31-34). In this study, the prevalence of co-infection SARS-CoV-2 with influenza A and B, clinical characterization, and chest radiography in co-infected patients with confirmed SARS-CoV-2 infection was meta-analyzed. The results indicated that the prevalence of influenza A is higher than influenza B co-infection in COVID-19 patients (2.3(0.5-9.3) vs. 0.1 (0.4-3.3)). Our findings show that fever and cough were the most common clinical symptoms (86% and 46%, respectively) in co-infected SARS-CoV-2 patients with influenza A or B. In addition, Fatigue, Diarrhea, and Difficult Breathing were the less common clinical findings among co-infected patients (13.8%, 12.2%, and 9.3%, respectively).

Influenza and SARS-Cov-2 viruses are transmitted by contact, droplets, and contaminated surfaces and cause respiratory diseases with a broad range of moderate to severe symptoms (35, 36). Based on the basic reproduction number R_0 , SARS-Cov-2 viruses can infect more people than influenza (1.5–5.7 for SARS-Cov-2, 0.9–2.1 for influenza) (36, 37). Several studies have confirmed co-infection of SARS-CoV-2 with influenza A and influenza B, such as studies in the United States (15, 16), China (17), and Iran (18). Some articles have shown that respiratory viruses such as influenza can lead to complications of the disease and even patient death in confirmed cases of COVID-19 (18-20). Some other research had the contrary view they assume that competitive advantage in virus connection can play an essential role in SARS-CoV-2 interactions with other viruses, such as influenza, during co-infection (38, 39). Moreover, different immune response mechanisms can give rise to a competitive advantage between SARS-COV-2 and other co-infecting viruses; therefore, in patients with SARS-CoV-2, the co-infection rate with other viruses, such as influenza, is much lower (38, 39).

The research limitations are the number of studies, small sample sizes, publication bias, heterogeneity of the study, poor quality analysis and reporting in some of the included studies.

Due to the low prevalence of SARS-CoV-2, co-infected influenza patients, and many differences between COVID-19 and influenza, such as transmissibility, mortality rate, laboratory diagnosis, and clinical symptoms (30, 40), these results only suggest that consider the influenza viruses in COVID-19 suspected patients. As a consequence, this approach will help to select the best treatment protocol for the management of COVID-19 patients and reduce the severity of the disease. People should also be vaccinated against seasonal influenza to reduce the risk of co-infection in the recent pandemic.

Declarations

Competing interests

The authors declare no competing interests.

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