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Co-infection of SARS-CoV-2 and influenza A/B among patients with COVID-19: a systematic review and meta-analysis

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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 result in co-infection with other pathogens such as influenza virus. This review investigates the co-infection of SARS-CoV-2 and influenza A/B among patients with COVID-19.

Methods This meta- analysis included 38 primary studies investigating co-infection of SARS-CoV-2 with influenza in confirmed cases of COVID-19. The global online databases were used to identify relevant studies published between December 2019 and July 2024. Data analysis was performed using STATA Ver. 17 software, and standard errors of prevalence were calculated using the binomial distribution formula. Heterogeneity of study results was evaluated using the I-square and Q index, and publication bias was examined using the Begg's and Egger's tests, as well as funnel plot. A random effects model was used to determine prevalence rates, and a forest plot diagram was used to present results with 95% confidence intervals. In addition, sensitivity analyses were performed to check the impact of each primary study on the overall estimate.

Result The analysis found that the prevalence of influenza in co-infected patients at 95% confidence interval using a random effect model was 14% (95% CI: 8–20%). Significant heterogeneity was observed in the random-effects model for influenza A, 11% (95% CI: 5-18%) and B, 4% (95% CI: 2-7%) in co-infected patients. The highest prevalence of influenza A/B (21%), influenza A (17%) and influenza B (20%) was shown in Asia and Europe respectively. Subgroup analysis by study year showed that the co-prevalence of COVID-19 and influenza A/B was similar in the pre-2021 and post-2021 time periods, at 14% (95% CI: 5-23%) for pre-2021 and 6-22% for 2021 and post-2021. Also, the overall prevalence of influenza A and B in COVID-19 patients is 11% and 4%, and there was no significant difference between the time periods before and after 2021. Meta-regression with a random-effects model showed that the variables location, year group, and total patients showed only 2.71% of very high heterogeneity ($I^2 = 99.92\%$), and none of these variables had a significant effect on the co-prevalence of COVID-19 and influenza A/B ($p > 0.05$). Also, meta-regression results showed that these variables had no significant effect on influenza A and B prevalence ($p > 0.05$) and showed

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only a small proportion of the very high heterogeneity ($I^2 = 99.72\%$), ($I^2 = 68.78\%$). In our study, Egger's test indicated that there was publication bias or small study effects in this meta-analysis ($p = 0.0000$).

Conclusion The combination of SARS-CoV-2 with influenza and other respiratory viruses requires the best treatment protocols to reduce the severity of the disease. In this approach, high vaccination coverage against seasonal influenza and SARS-CoV-2 could reduce the risk of co-infection in the recent pandemic.

Keywords SARS-CoV-2, Co-infection, COVID-19, Influenza virus A, Respiratory syndrome coronavirus 2, Coronavirus, Influenza virus B

Introduction

Coronaviruses are a family of RNA viruses that can cause a spectrum of diseases from the common cold to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) with mortality rates of 10% and 3%, respectively [1, 2]. 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 spread all over the world from 31 December and spread across the continents [3]. The first countries to announce the COVID-19 outbreak as a public health problem included China, South Korea, and Iran [4]. The symptoms of COVID-19 are fever, cough, sore throat, fatigue, shortness of breath, and gastrointestinal symptoms such as diarrhea and nausea [5]. Coronaviruses have been responsible for the common cold for a long time and the symptoms of SARS-CoV-2 disease in humans are similar to the common cold or influenza. However, the infection and mortality rate of SARS-CoV-2 are much higher than other respiratory infections. SARS-CoV-2 is a contagious virus and can spread from an infected person's breath, cough, sneeze or via airborne transmission [6]. SARS-CoV-2 may have co-infection with other pathogens such as viruses, bacteria, and fungi, which increases hospitalization and mortality rates. Influenza is a co-infection that commonly occurs alongside COVID-19 [7]. It is a respiratory illness, and its symptoms include fever, chills, body aches, sore throats, fatigue, vomiting, abdominal pain, diarrhea, nasal symptoms, loss of taste, and chest pain. It seems that COVID-19 and SARS have many similar features for transmission and immune-pathogenesis [8–10]. Several studies from the United States [11], China [12], and Iran [13] reported SARS-CoV-2 co-infection with influenza A and B viruses.

Because co-infections with respiratory viruses (such as SARS-CoV-2 and influenza) can worsen disease severity and complicate clinical management, these co-infections are of great concern [14]. Multiple pathogens can cause immune overload, with the body's immune response having an insufficient response to either virus when faced with these co-infections [14, 15]. In patients co-infected with both SARS-CoV-2 and influenza A virus, this phenomenon can worsen respiratory symptoms such as pneumonia, sinus infection, bronchitis, and cardiovascular disease and increase the risk for severe respiratory failure [16, 17]. The mechanisms of co-infection severity can be complex [16, 18]. When the immune system is activated against multiple viral pathogens at the same time, immune overload occurs and the immune response can become overly inflamed [19]. This dysregulation of the immune system can lead to greater lung tissue damage and a greater susceptibility to acute respiratory distress [19, 20]. In co-infected individuals, either virus can promote replication and pathogenicity of the other, making the clinical picture more difficult to interpret [21]. Also, diagnosing co-infections is a big problem in clinical settings [21]. COVID-19 is caused by SARS-CoV2, and its symptoms are similar, but not the same, as those of influenza, an important feature for accurate diagnosis, so that proper treatment can be given [22]. In cases of co-infection, diagnostic assays may find it hard to distinguish between these viruses [22]. Multiplex PCR panels have been identified as a method to improve the detection of multiple respiratory viruses, but concerns about specificity and sensitivity make clinical management of patients, challenging [23].

Co-infections are present and, because of these, can worsen outcomes and are associated with increased rates of hospitalization and mortality [24]. A report showed that coronavirus co-infections — those with SARS-CoV-2 and influenza — had significantly more severe respiratory problems and worse overall clinical outcomes than those only infected with one of the viruses. Vigilant monitoring, rapid identification of co-infections and guided effective treatment strategies are required to reduce the risk of severe complications [25].

Evidence suggests that co-infections with other respiratory viruses, such as SARS-CoV-2 and influenza, are concerning as they involve immune overload and diagnostic difficulties complicating prognosis and treatment, and predisposing individuals to severe respiratory illness. Such cases require improved patient outcomes through effective monitoring, assuming a high index of suspicion of co-infections, and utilizing an advanced diagnostic technique. Current research provides a better understanding of the actual infection rate of co-infection with SARS-CoV-2 and influenza virus.

Methods

The present meta-analysis was described by the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA-P) statement and the guidelines of the Meta-analysis of Observational Studies in Epidemiology.

Search strategy

Electronic databases, including Web of Science, Science Direct, Scopus, PubMed, ProQuest, and Google Scholar search engine were searched to find relevant articles published in December 2019-July 2024. The search keywords included 'Co-infection', 'SARS-CoV-2', 'COVID-19', 'SARS-CoV-2', 'severe acute respiratory syndrome coronavirus 2', 'coronavirus disease 2019 virus', '2019 novel coronavirus', 'Influenza B viruses', 'Influenza virus type B', 'Influenza Viruses Type B', 'Influenza A viruses', 'Influenza virus type A' with combination "OR", "AND" and "NOT" Boolean Operators in the Title/Abstract/Keywords field (Appendix 1). The reference list of all related studies was also reviewed for any other related publications. The search was restricted to original articles/abstracts published in the English language that reported co-infection of SARS-CoV-2 and influenza A/B among patients with COVID-19. Screening, data extraction, study selection, data extraction, and quality assessment were done by two authors (HJA and MRT) and any disagreements with article selection were resolved through discussion, and a third author (TM) was available to resolve the disagreement. In addition, the article references were screened to find additional related studies and increase search sensitivity. Finally, all collected references are entered into reference management software (EndNote).

Inclusion criteria

The PI(E)CO process (Population, Exposure, Comparison, and Outcomes) was adopted to define inclusion and exclusion criteria for study selection. "P" signifies patients with SARS-CoV-2; "E" expose with influenza virus; "O" means the evaluation of co-infection of influenza A/B in patients with SARS-CoV-2. All cross-sectional studies were entered into this meta-analysis for evaluation. All articles with sufficient quality scores that met the study inclusion criteria were selected. The inclusion criteria were as follows:

1) Studies published in English.
2) Studies that included patients with a confirmed diagnosis of COVID-19.
3) Studies based on the prevalence of influenza A in COVID – 19 patients.
4) Studies based on the prevalence of influenza B in COVID – 19 patients.
5) Studies that included patients with a confirmed diagnosis of influenza.

Exclusion criteria

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

Study selection

First, the full text or summary of articles, documents, and reports is extracted. Then, duplicates and irrelevant articles were excluded from this study. Next, the case reports and review studies were removed from this meta-analysis. Finally, data was extracted from full-text articles based on inclusion and exclusion criteria.

Quality assessment

After identification and screening of studies, articles were assessed for eligibility, and suitable studies were included in the meta-analysis review. The Newcastle–Ottawa scale (NOS) checklist was used for evaluation of the quality of selected articles based on titles and contents. The NOS checklist is composed of 7 items that cover all aspects of methodology, such as collection methods, sample size, statistical analysis tests, study objectives, comparability and study population. Based on the results of quality assessment, studies were divided into 4 categories: very good studies: 9–10 points, good studies: 7–8 points, satisfactory studies: 5–6 points, and unsatisfactory studies: 0 to 4 points. Studies with low-quality scores were excluded from the final meta-analysis [26, 27].

Data extraction

The following variables were extracted: first author, publication date, type of study, geographical regions, study language, total number of COVID-19 patients, total number of influenza A, total number of influenza B were entered into the excl.

Statistical analysis

Information preparation was done in a Microsoft Excel spreadsheet and all statistical analyses were carried out in STATA Ver. 17 software. In this study, the primary outcome was to understand the prevalence of influenza in COVID-19 patients.

Data were weighted and combined based on the inverse variance. Cochran (Q) and I^2 tests were used to determine the heterogeneity index between studies and a 95% confidence interval (CI) was used to interpret the results. I^2 values of 25%, 50%, and 75% represented a low, moderate, and high degree of heterogeneity, respectively. A meta-regression test was used to assess the prevalence of influenza on heterogeneity. To assess publication bias, an Egger's and Begg test was performed, and a funnel plot

with a significant level of < 0.1 was used to evaluate the publishing bias. In addition, sensitivity analyses were performed to check the impact of each primary study on the overall estimate.

Results

A total of 1031 articles were obtained using the electronic search strategy. Subsequently, 789 duplicated records on the same study were excluded. Thereafter, 78 articles were omitted due to having an irrelevant title and/or abstract. After removing case series and review articles, finally, according to the NOS (Newcastle-Ottawa Scale) guideline, 38 studies were included in the meta-analysis according to the inclusion and exclusion criteria (Table 1). Figure 1 shows the review process for the included studies.

Co-infection of COVID-19 and influenza A/B

Based on the heterogeneity between the results of the primary studies ($I^2 = 99.9$, $Q = 5570.66$), the random-effects model was used for assessment (Fig. 2).

The presented forest plot shows the combined prevalence of co-infection with both influenza types (A and B) in COVID-19 patients. The estimated overall prevalence, using a random-effects model, is 14% (95% CI: 8–20%), meaning that approximately 14% of COVID-19 patients are co-infected with both types of influenza. The analysis shows significant heterogeneity between studies, as indicated by an I^2 statistic of 99.97%. This value indicates that almost all the observed variability is due to differences between studies and cannot be attributed to random chance. The Q test for heterogeneity also confirms this ($p < 0.05$). This high heterogeneity is likely due to a variety of reasons, including methodological differences, geographic variation, temporal variation in study periods, and differences in diagnostic criteria.

Subgroup analysis for influenza A/B prevalence by geographical regions

Forest Plot analysis of subgroups by geographic region (Asia, Africa, Americas, and Europe) clearly shows that the co-prevalence of COVID-19 and influenza (A and B) varies significantly between regions (Fig. 3). In the Asian region, the combined prevalence of influenza A/B was estimated to be 21% (95% CI: 11-30%). This region, with the highest prevalence, has very high heterogeneity (I^2 = 99.91%), which is likely related to reasons such as differences in diagnostic methods, characteristics of the studied population, and the greater coincidence of COVID-19 and influenza epidemics in this region. Multiple studies in Asia, with mixed results, have played a significant role in the high heterogeneity in this region. In contrast, the African region shows the lowest value with a combined prevalence of 3% (95% CI: -3-8%). Heterogeneity in this region is zero (I^2 = 0%), but the limited number of studies in Africa prevents strong and precise conclusions about the true prevalence. This low prevalence may be due to a lack of sufficient data, limited laboratory infrastructure, or underreporting of cases. In the Americas, the combined prevalence is 6% (95% CI: 0–13%). Although the reported prevalence in this region is lower than in Asia, there is very high heterogeneity (I^2 = 99.97%). This indicates wide differences in study results in this region, including some very wide confidence intervals. Variation in sample size, diagnostic methods, and population conditions may play a key role in this heterogeneity. In Europe, the combined prevalence is reported to be 15% (95% CI: 2–29%). This region also has high heterogeneity (I^2 = 93.46%), but it appears that fewer studies have been conducted in this region. This prevalence is lower than in other regions, especially Asia, but the wide confidence interval suggests that further studies are needed to make a more precise estimate.

Subgroup analysis for influenza A/B prevalence by period time

Subgroup analysis by study year showed that the co-prevalence of COVID-19 and influenza A/B was similar in the pre-2021 and post-2021 time periods, at 14% (95% CI: 5-23%) for pre-2021 and 6-22% for 2021 and post-2021. However, heterogeneity was very high in both time periods (I^2 = 99.83% and I^2 = 99.97%), indicating wide differences between studies (Fig. 4).

Sensitivity analysis for influenza A/B

Sensitivity analysis was performed by removing six influential studies, including Nowak (2020) and David Kim (2020) due to a prevalence of 0.00 and a non-significant confidence interval, Wei Xia (2020) and David D. Zhang (2020) due to a very wide confidence interval, and Yue (2020) and Ma S (2020) due to a very high prevalence (57% and 49%) (Fig. 5).

After removing these studies, the overall co-prevalence of COVID-19 and influenza remained stable (14%, 95% CI: 8-21%), indicating the stability of the results. However, heterogeneity remained very high (I^2 = 99.96%), indicating that major sources of heterogeneity such as geographical differences and diagnostic methods still remained across studies. These results highlight the importance of supplementary analysis to identify factors contributing to heterogeneity.

Publication bias for influenza A/B prevalence

Funnel plots show relative symmetry in studies with larger sample sizes, but asymmetry in the lower part may indicate publication bias. This finding requires statistical evaluation using Egger or Begg tests and correction methods. Egger's regression test for small studies showed

Table 1 Table of quality assessment results of primary studies included in the systematic review and meta-analysis based on the NOS checklist

Selection					Comparability	Outcome		Score
Reference	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Comparability of subjects in different outcome groups on the basis of design or analysis. Confounding factors controlled.	Assessment of outcome	Statistical test	
Castillo (2020) [59]	×			××	××	××		7
Ma(2020) [60]	×			××	××	××	×	8
Nowak (2020) [61]	×	×		××	×	××		7
Ding (2020) [62]	×			××	××	×	×	7
Hashemi1 (2020) [63]	×			××	××	××		7
Yue (2020) [33]	×			××	××	××	×	8
Ma S (2020) [64]	×			××	××	××	×	8
Zhua(2020) [65]	×			××	××	××	×	8
Yuan Cheng (2020)	×			××	××	××	×	8
María Luisa Blasco (2020)	×			××	×	××		6
Damien Contou (2020) [66]	×			××	××	××		7
Wei Xia (2020) [67]	×			××	××	×		6
David D. Zhang (2020) [35]	×			×	×	××		5
Qin Wu (2020) [68]	×			××	××	××	×	8
Ying Li (2020) [69]	×			××	××	××	×	8
David Kim (2020) [34]	×			××	××	××	×	8
Aniruddha Hazra (2020) [36]	×				×	××	×	5
A. Agarwal (2021) [70]	×			××	×	××		6
Bandar Alosaimi (2021) [44]	×			××	××	××	×	8
Kyoung Ho Roh (2021) [71]	×				×	××	×	5
Man-Ling Tang (2021) [72]	×			××	××	××	×	8
Nicolas Allou (2021) [73]	×			××	××	××	×	8
Xunliang Tong (2021) [74]	×			××	××	××	×	8
Fiona Pigny (2021) [30]	×			×	×	××		5
Hsing-Yi Chung (2021) [31]	×			×	×	××	×	6
Patricia Schirmer (2021) [75]	×			××	××	××	×	8
Ana Karolina Antunes Eisen (2021) [37]	×			×	×	××		5
Natalie C. Marshall (2021) [38]	×	×		××	××	××	×	9
So Young Kim (2021) [76]	×	×		××	××	××	×	9
Cynthia Y. Tang (2022) [77]	×			×	××	××	×	7
Eggi Arguni (2022) [78]	×				××	××		5
Matheus Negri Boschiero (2022) [40]	×			×	××	××	×	7
Ishan Garg (2022) [79]	×	×		××	××	×	×	8
Moussa Lingani (2022) [29]	×			××	××	××	×	8
Dennis Minoru Fujita (2022) [80]	×	×			××	×		5

Table 1 (continued)

Selection					Comparability	Outcome		Score
Reference	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Comparability of subjects in different outcome groups on the basis of design or analysis. Confounding factors controlled.	Assessment of outcome	Statistical test	
Aušra Steponavičienė (2023) [39]	×	×		×	××	××	×	8
Jeong-Hwan Hwang (2023) [81]	×	×		××	××	××	×	9
Sushmitha Anand (2023) [32]	×			××	×	××		6

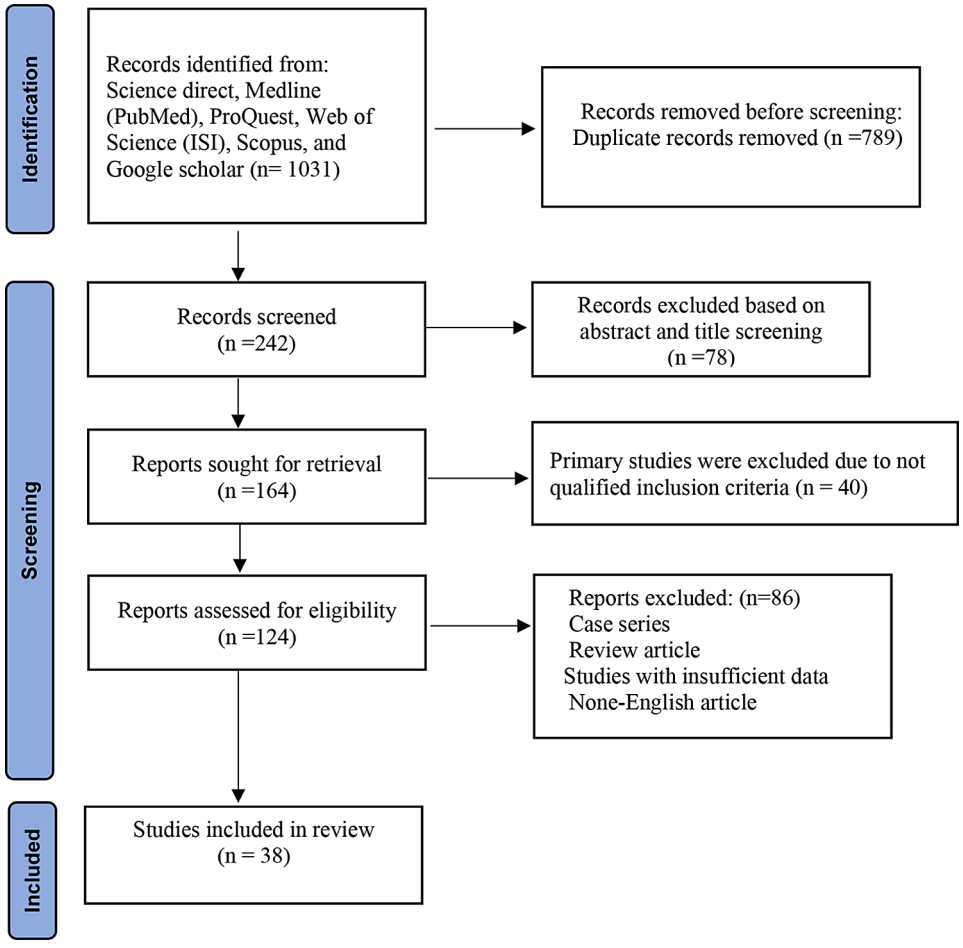

Fig. 1 The search strategy and flow diagram for databases, screening and selection of primary studies in the systematic review and meta-analysis

the beta1 value (5.02) with a standard error (1.16) and the z value was significant (z = 4.33, $p < 0.0001$). These results indicate the presence of publication bias in this meta-analysis (Fig. 6).

Meta regression analysis for influenza A/B prevalence

Meta-regression with a random-effects model showed that the variables location, year group, and total patients showed only 2.71% of very high heterogeneity (I^2 = 99.92%), and none of these variables had a significant effect on the co-prevalence of COVID-19 and influenza A/B ($p > 0.05$). The remaining heterogeneity was significant (Q_res, $p < 0.0001$), suggesting that other factors, such as methodological differences or demographic conditions, may have influenced the results.

Co-infection of COVID-19 and influenza A

Of the 33 studies selected for the present systematic review/meta-analysis, the Co-infection of SARS-CoV-2 and influenza A was reported in 417 patients. The

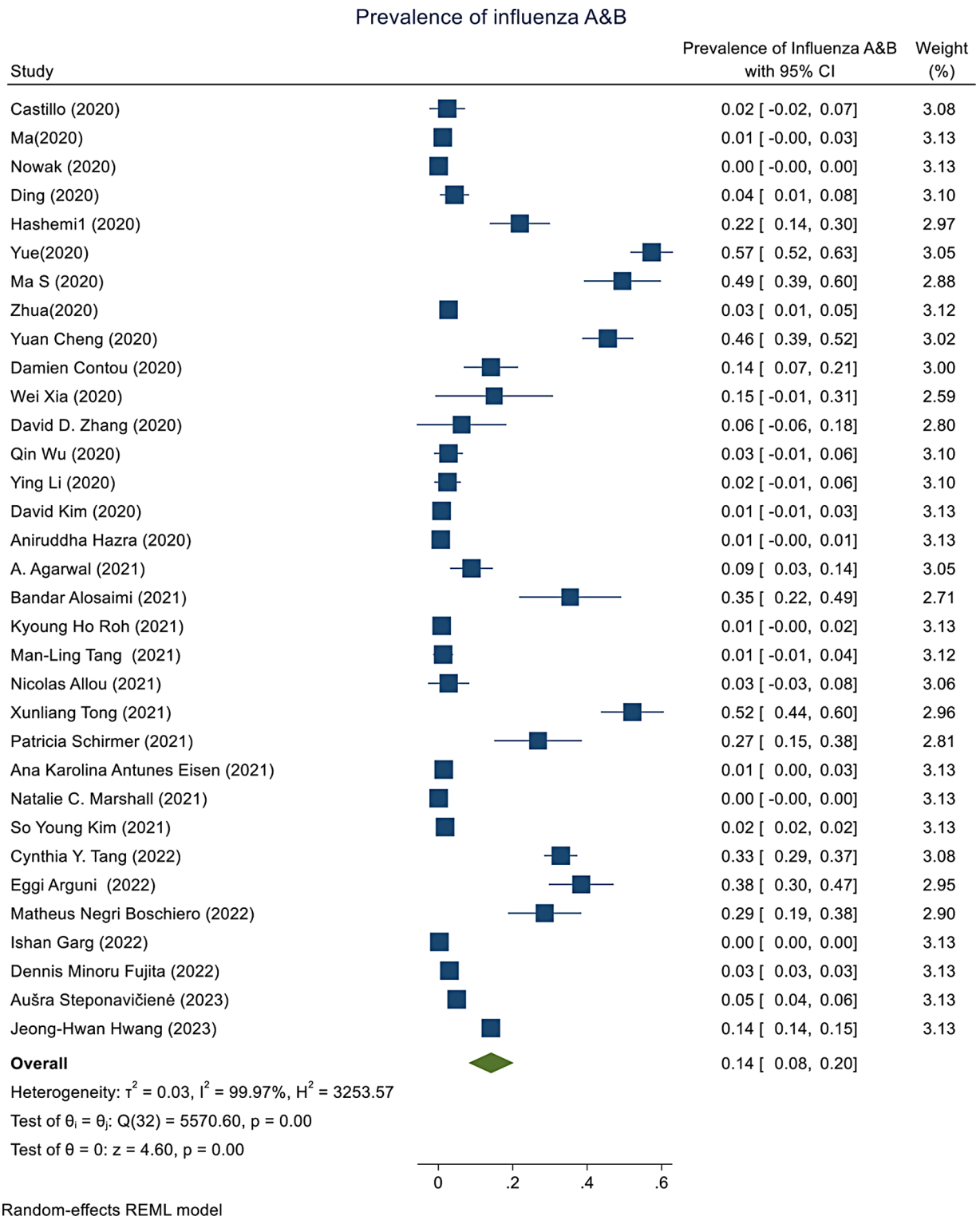

Fig. 2 Forest plot diagram for estimation of total prevalence of influenza A/B in COVID-19 patients according to each primary studies and overall estimate with a 95% confidence interval

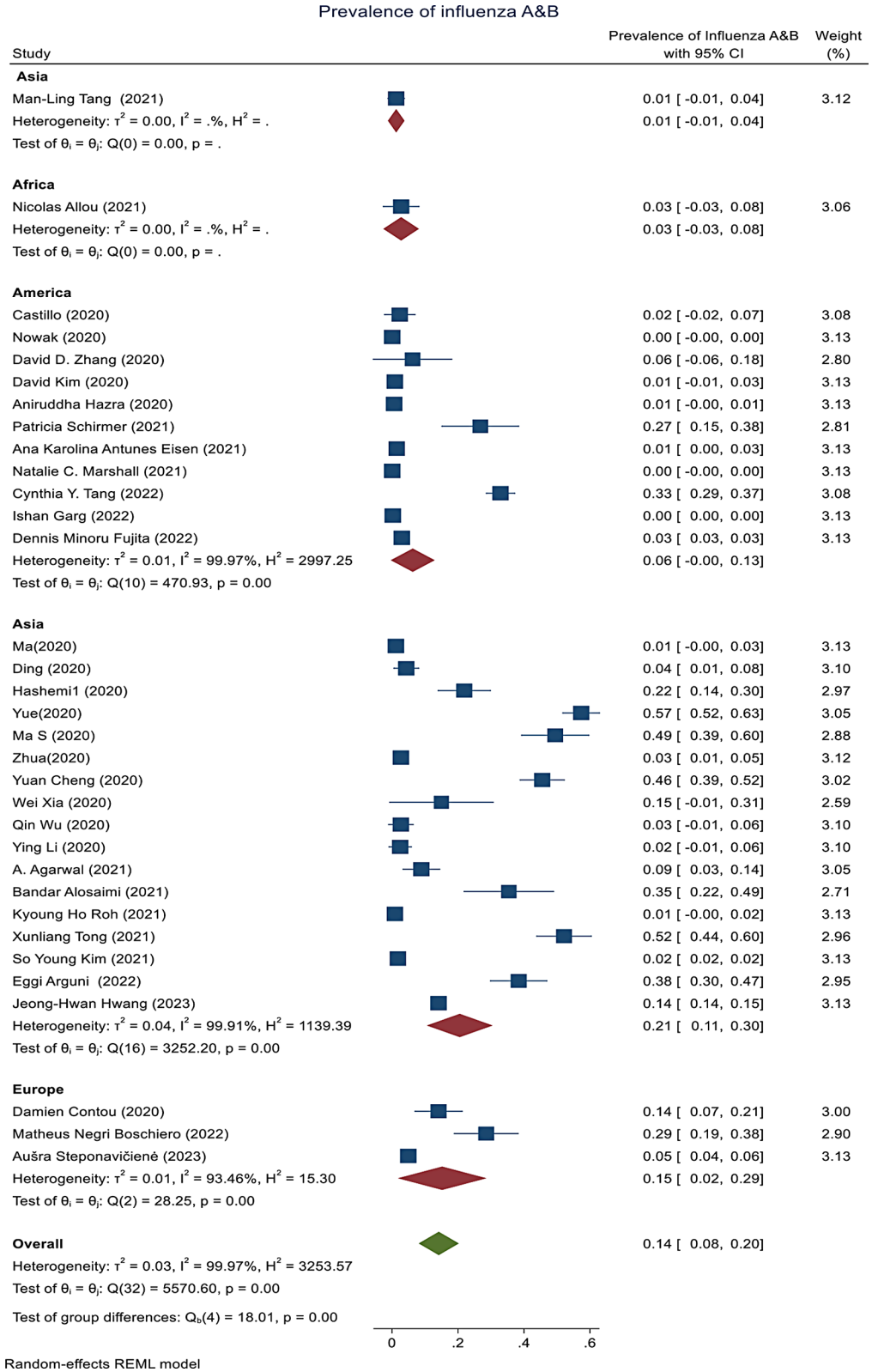

Fig. 3 Overall results of forest plot subgroup analysis for influenza A/B prevalence by geographic region (Asia, Africa, America and Europe)

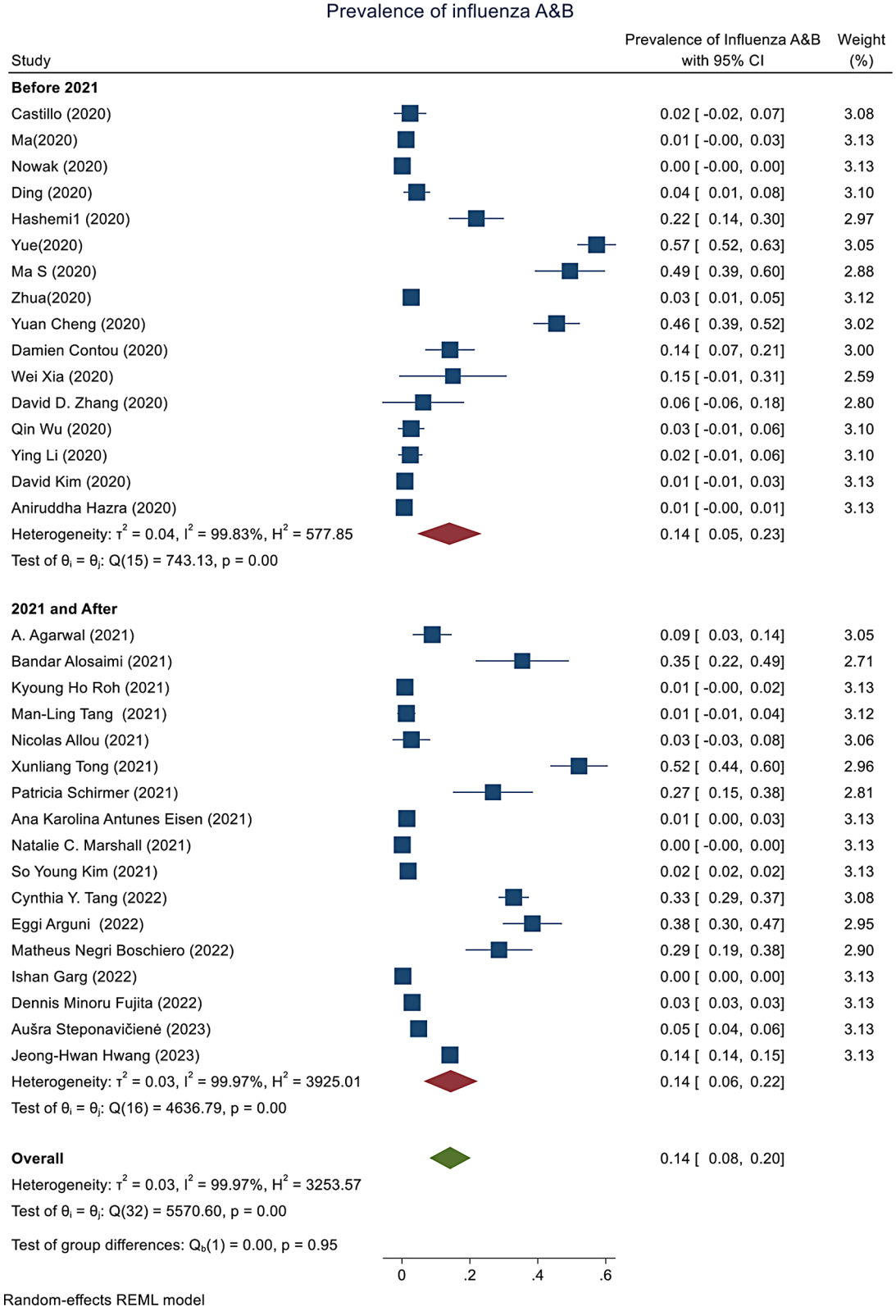

Fig. 4 Overall Forest Plot results for influenza A/B prevalence by time period (before and after 2021)

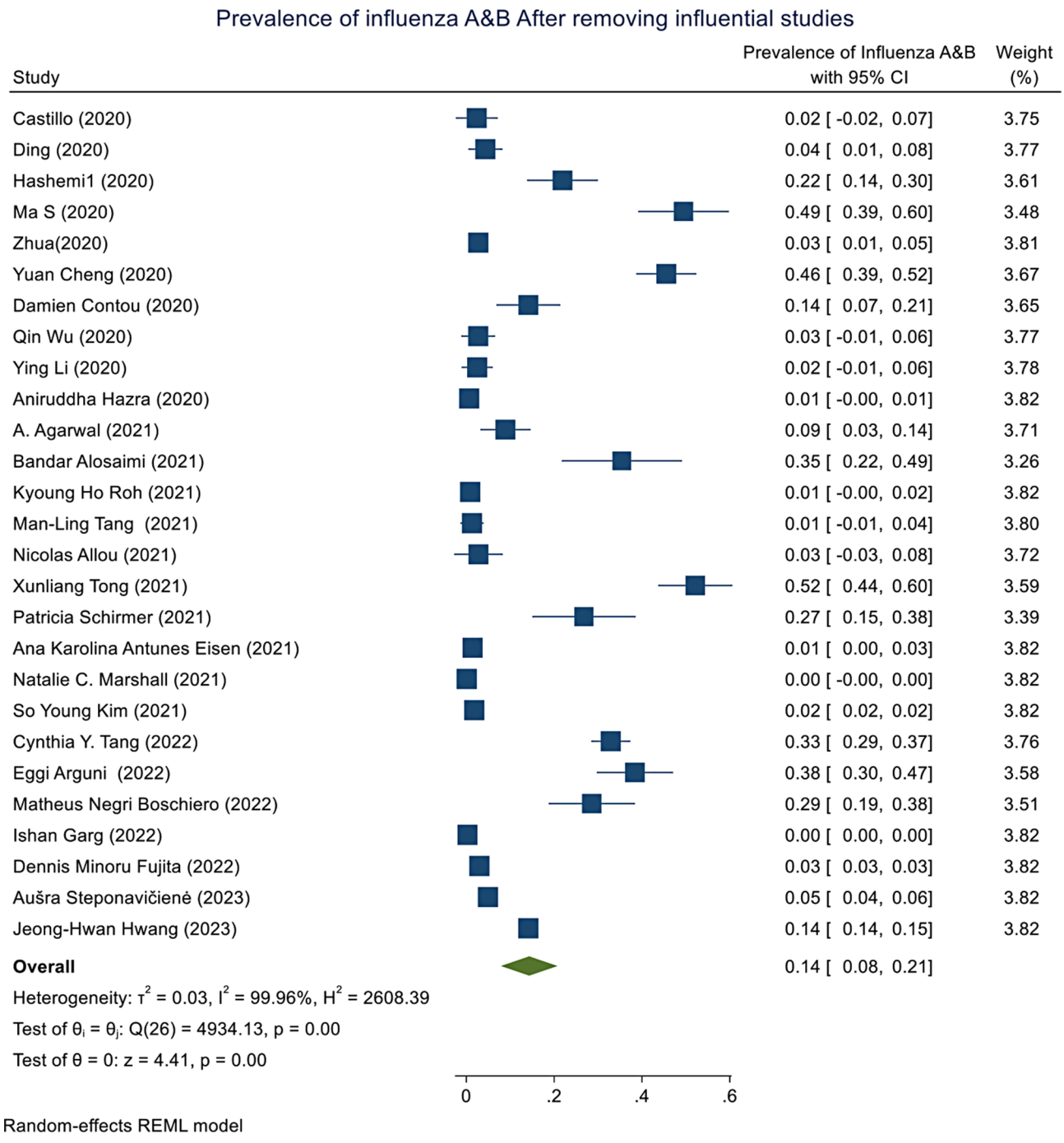

Fig. 5 Forest plot diagram for estimation of influenza A/B prevalence sensitivity analysis according to each primary study and overall estimate with a 95% confidence interval

prevalence of co-infection with influenza in COVID-19 patients varied from 0 [28–32] to 49.83% in the Yue study [33]. (Table 2). The overall prevalence of influenza A is estimated to be 11% (95% CI: 5-18%), but the very high heterogeneity (I^2 = 99.93%) indicates significant differences between studies. These differences are likely due to factors such as diagnostic methods, geographic region, or patient demographics (Fig. 7).

Subgroup analysis for influenza A prevalence by geographical regions

The prevalence of influenza A in COVID-19 patients varied by geographic region. The highest prevalence is shown in Asia (17%) and the lowest in Africa and America (3% and 0%). High heterogeneity in Asia (I^2 = 99.63%) indicates significant variation between studies in this region, while Europe and Africa had very low

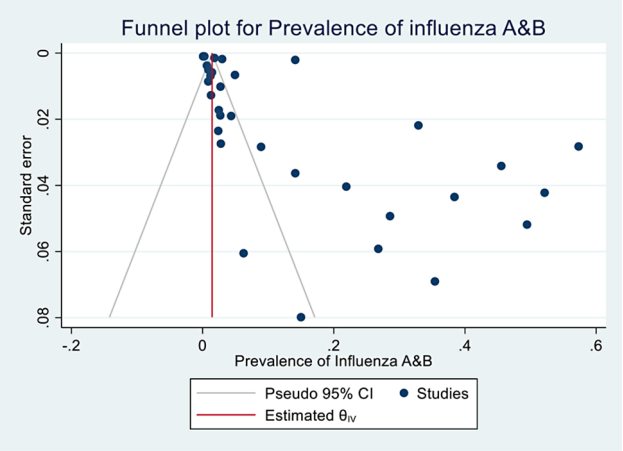

Fig. 6 Funnel plot to investigate publication bias in prevalence of influenza A/B in COVID-19 patients

heterogeneity. These differences may be related to methodological reasons, geographic differences, and demographic characteristics (Fig. 8).

Subgroup analysis for influenza A prevalence by period time

The overall prevalence of influenza A in COVID-19 patients is 11%, and there was no significant difference between the time periods before and after 2021. In both time periods, there was very high heterogeneity (I^2 > 99%), likely due to differences in methodology, demographic characteristics, and diagnostic methods (Fig. 9).

Publication bias for influenza A prevalence

Egger's test indicated that there was publication bias or small study effects in this meta-analysis ($p = 0.0001$). This finding, together with the asymmetry observed in the Funnel Plot, suggests that studies with high prevalence may be over-published and studies with low prevalence under-reported. This should be considered when interpreting the results of the meta-analysis (Fig. 10).

Meta regression analysis for influenza A prevalence

Meta-regression results showed that the variables location, year group, and total patients had no significant effect on influenza A prevalence ($p > 0.05$) and showed only a small proportion of the very high heterogeneity (I^2 = 99.72%). These findings suggest that other factors, such as methodological differences, geographical conditions, or patient demographic characteristics, may be responsible for the remaining heterogeneity.

Co-infection of COVID-19 and influenza B

Of 12 studies selected for the present systematic review/meta-analysis, the Co-infection of SARS-CoV-2 and Influenza B was reported in 51 patients. The prevalence of co-infection with influenza in COVID-19 patients varied from 0 [29, 31, 32, 34–39] to 20.2% in Matheus study [40].(Table 2). The overall prevalence of influenza B is estimated to be 4% (95% CI: 2-7%), but the very high heterogeneity (I^2 = 92.38%) indicates significant differences between studies. These differences are likely due to some factors such as diagnostic methods, geographic region, or patient demographics (Fig. 11).

Subgroup analysis for influenza B prevalence by geographical regions

The prevalence of influenza B in COVID-19 patients varied by geographic region. The highest prevalence is shown in Europe (20%) and the lowest in Asia (1%). These differences may be related to methodological reasons, geographic differences, and demographic characteristics (Fig. 12).

Subgroup analysis for influenza B prevalence by period time

The overall prevalence of influenza B in COVID-19 patients is 4%, and there was no significant difference between the time periods before and after 2021. In both time periods, there was very high heterogeneity (I^2 > 99%), likely due to differences in methodology, demographic characteristics, and diagnostic methods (Fig. 13).

Publication bias for influenza B prevalence

Egger's test indicated that there was publication bias or small study effects in this meta-analysis ($p = 0.0000$). This finding, together with the asymmetry observed in the Funnel Plot, suggests that studies with high prevalence may be over-published and studies with low prevalence under-reported. This should be considered when interpreting the results of the meta-analysis (Fig. 14).

Meta regression analysis for influenza B prevalence

Meta-regression results showed that the variables location, year group, and total patients had no significant effect on influenza A prevalence ($p > 0.05$) and showed only a small proportion of the very high heterogeneity (I^2 = 68.78%). These findings suggest that other factors, such as methodological differences, geographical conditions, or patient demographic characteristics, may be responsible for the remaining heterogeneity.

Discussion

Given the significance of this issue, in this meta-analysis, the prevalence of influenza in co-infected patients with a 95% confidence interval using a random effect model was 14% (95% CI: 8–20%). In the present study, the prevalence estimates for each study vary widely, from a low of 0.00 to a high of 57%, and some studies have wide confidence intervals. These variations may reflect differences

Table 2 Estimation of influenza prevalence in COVID-19 patients

Reference	Authors	Location of study	Number of SARS-CoV-2 patients	Number of patients with total influenza (*N*/%)	Number of patients with influenza A (*N*/%)	Number of patients with influenza B (*N*/%)
[59]	Castillo (2020)	USA	42	1 (2.38)	1(2.38)	N/A
[60]	Ma(2020)	China	250	3 (1.2)	2 (0.8)	1 (0.4)
[61]	Nowak (2020)	USA	1204	1 (0.08)	1 (0.08)	N/A
[62]	Ding (2020)	China	115	5 (4.34)	3 (2.60)	2 (1.73)
[63]	Hashemi1 (2020)	Iran	105	23 (21.90)	23 (21.90)	N/A
[33]	Yue(2020)	China	307	176 (57.32)	153 (49.83)	23 (7.49)
[64]	Ma S (2020)	China	93	46 (49.46)	44 (47.31)	2 (2.15)
[65]	Zhua(2020)	China	257	7 (27.23)	2 (0.7)	5 (1.94)
[82]	Yuan Cheng (2020)	China	213	97 (45.53)	97 (45.53)	N/A
[28]	María Luisa Blasco (2020)	Spain	103	0 (0)	0 (0)	N/A
[66]	Damien Contou (2020)	French	92	13 (14.13)	N/A	N/A
[67]	Wei Xia (2020)	China	20	3 (15)	1 (5)	2 (10)
[35]	David D. Zhang (2020)	Chicago	16	1 (6.25)	1 (6.25)	0
[68]	Qin Wu (2020)	China	74	2 (2.7)	1 (1.35)	1 (1.35)
[69]	Ying Li (2020)	China	81	2 (2.46)	1 (1.23)	1 (1.23)
[34]	David Kim (2020)	California	116	1 (0.8)	1 (0.8)	0 (0)
[36]	Aniruddha Hazra (2020)	Chicago	459	3 (0.6)	3 (0.6)	0 (0)
[70]	A. Agarwal (2021)	India	101	9 (8.91)	9 (8.91)	N/A
[44]	Bandar Alosaimi (2021)	Saudi Arabia	48	17 (35.41)	17 (35.41)	N/A
[71]	Kyoung Ho Roh (2021)	Korea	342	3 (0.9)	3 (0.9)	N/A
[72]	Man-Ling Tang (2021)	China	78	1 (1.28)	N/A	1 (1.28)
[73]	Nicolas Allou (2021)	Reunion island	36	1 (2.77)	1 (2.77)	N/A
[74]	Xunliang Tong (2021)	China	140	73 (52.14)	N/A	N/A
[30]	Fiona Pigny (2021)	Geneva	51	0 (0)	0 (0)	N/A
[31]	Hsing-Yi Chung (2021)	Taiwan	55	0 (0)	0 (0)	0 (0)
[75]	Patricia Schirmer (2021)	USA	56	15 (26.78)	12 (21.42)	3 (5.35)
[37]	Ana Karolina Antunes Eisen (2021)	Brazil	418	6 (1.43)	6 (1.43)	0 (0)
[38]	Natalie C. Marshall (2021)	Canada	1141	1 (0.08)	1 (0.08)	0 (0)
[76]	So Young Kim (2021)	Korea	8070	146 (1.8)	N/A	N/A
[77]	Cynthia Y. Tang (2022)	USA	462	152 (32.90)	N/A	N/A
[78]	Eggi Arguni (2022)	Indonesia	125	48 (38.4)	32 (25.6)	16 (12.8)
[40]	Matheus Negri Boschiero (2022)	Portugal	84	24 (28.57)	5 (5.95)	17 (20.2)
[79]	Ishan Garg (2022)	USA	1,659,040	4501 (0.27)	N/A	N/A
[29]	Moussa Lingani (2022)	Africa	324	0 (0)	0 (0)	0 (0)
[80]	Dennis Minoru Fujita (2022)	Brazil	8877	264 (2.97)	N/A	N/A
[39]	Aušra Steponavičienė (2023)	Lithuania	1074	53 (4.93)	53 (4.93)	0 (0)
[81]	Jeong-Hwan Hwang (2023)	Korea	28,338	4003 (14.12)	N/A	N/A
[32]	Sushmitha Anand (2023)	India	100	0(0)	0(0)	0(0)
Total			1,712,413	9622	417	51

in sample sizes, testing strategies, and characteristics of the study population. Studies with larger sample sizes, such as those in the center of the graph, carry more weight in the overall estimate, while smaller studies with greater uncertainty have less impact on the overall result. The high heterogeneity observed in this analysis requires caution in interpreting the combined prevalence. This suggests that it is necessary to conduct subgroup analysis to examine possible sources of this heterogeneity (such as geographic region, year of publication, or diagnostic methods). Also, sensitivity analysis that exclude studies with extreme prevalence values or wide confidence intervals can confirm the robustness of the results. Despite the observed variability, the combined prevalence estimates highlight the clinical and public health importance of co-infections during COVID-19. Co-infections with influenza and SARS-CoV-2 may increase the severity of illness, complicate treatment management, and put more pressure on health systems.

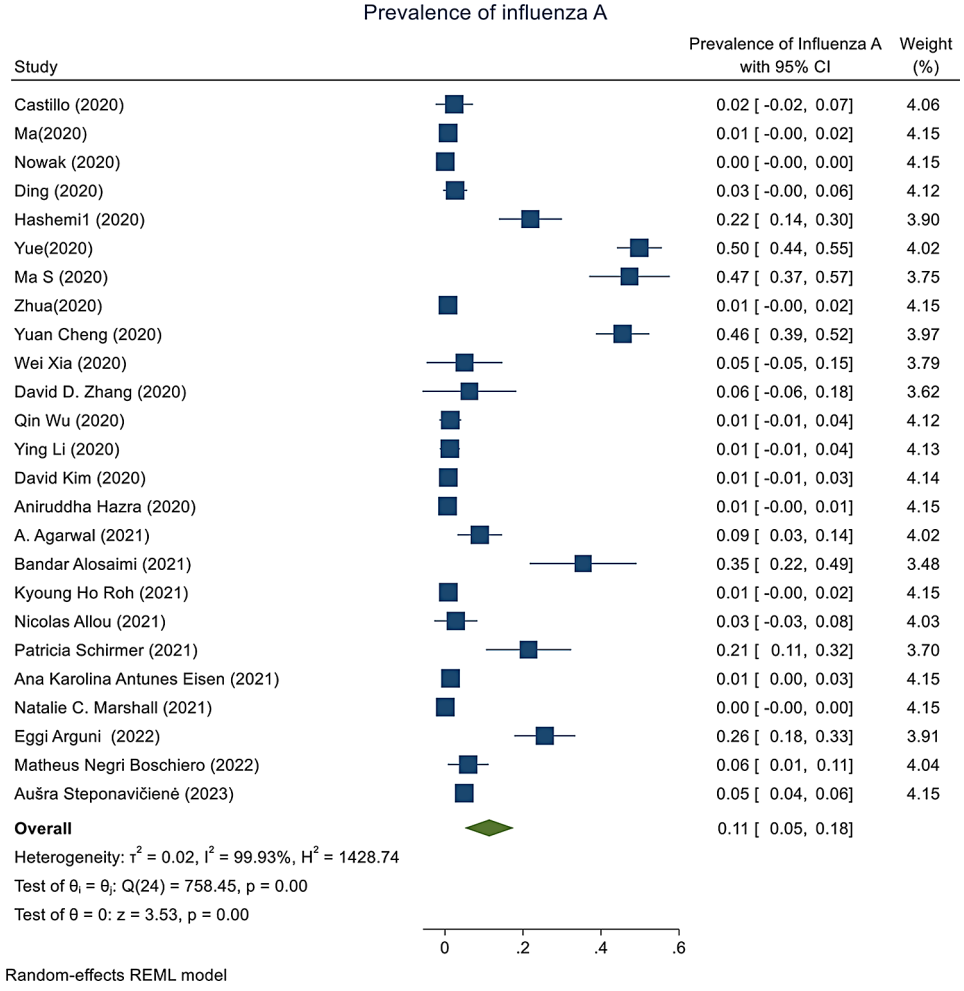

Fig. 7 Forest plot diagram for estimation of influenza A prevalence in COVID-19 patients according to each primary studies and overall estimate with a 95% confidence interval

According to certain studies, concurrent SARS-CoV-2 and influenza virus infection was more prevalent during the initial SARS-CoV-2 epidemic in China and involved patients were at greater risk for poor health outcomes [41].

Generally, co-infection is thought to affect illness outcomes and cause more severe symptoms [42]. For example, respiratory viruses such as influenza can lead to complications of the disease and even patient death in confirmed cases of COVID-19 [17]. The clinical features of COVID-19 individuals who were also infected by influenza were similar to those of individuals with a single SARS-CoV-2 infection, but the clinical prognosis was higher in co-infected patients [43]. Contrary to some studies, SARS-COV-2 co-infection with influenza, particularly the influenza B virus, can lead to poor outcomes. This disparity could be due to a complex process including how co-infection impacts clinical outcomes [41]. A study based on mathematical models found that co-infection of influenza with SARS-CoV-2 increases the chance of cross-species transmission and pandemics. Therefore, early detection and prevention of concurrent influenza and SARS-CoV-2 infection may play a key role in pandemic control [44].

This analysis showed that the co-infection rate with influenza A was higher than influenza B in SARS-CoV-2 patients. A number of biological characteristics and epidemiological factors can explain why co-infection rates of SARS-CoV-2 with influenza A are higher than with influenza B [15]. Generally, influenza A viruses have a broader host range and are able to mutate rapidly to the point that they exhibit larger seasonality and do fewer major outbreaks than influenza B [45, 46]. Such higher adaptability might also contribute to an increased prevalence and concomitant infections in populations during the time of peak flu season [46]. Influenza A is responsible for more extensive outbreaks and is more aggressive, while influenza B is more likely to cause seasonal flu [47]. At the height of respiratory illness, especially in colder

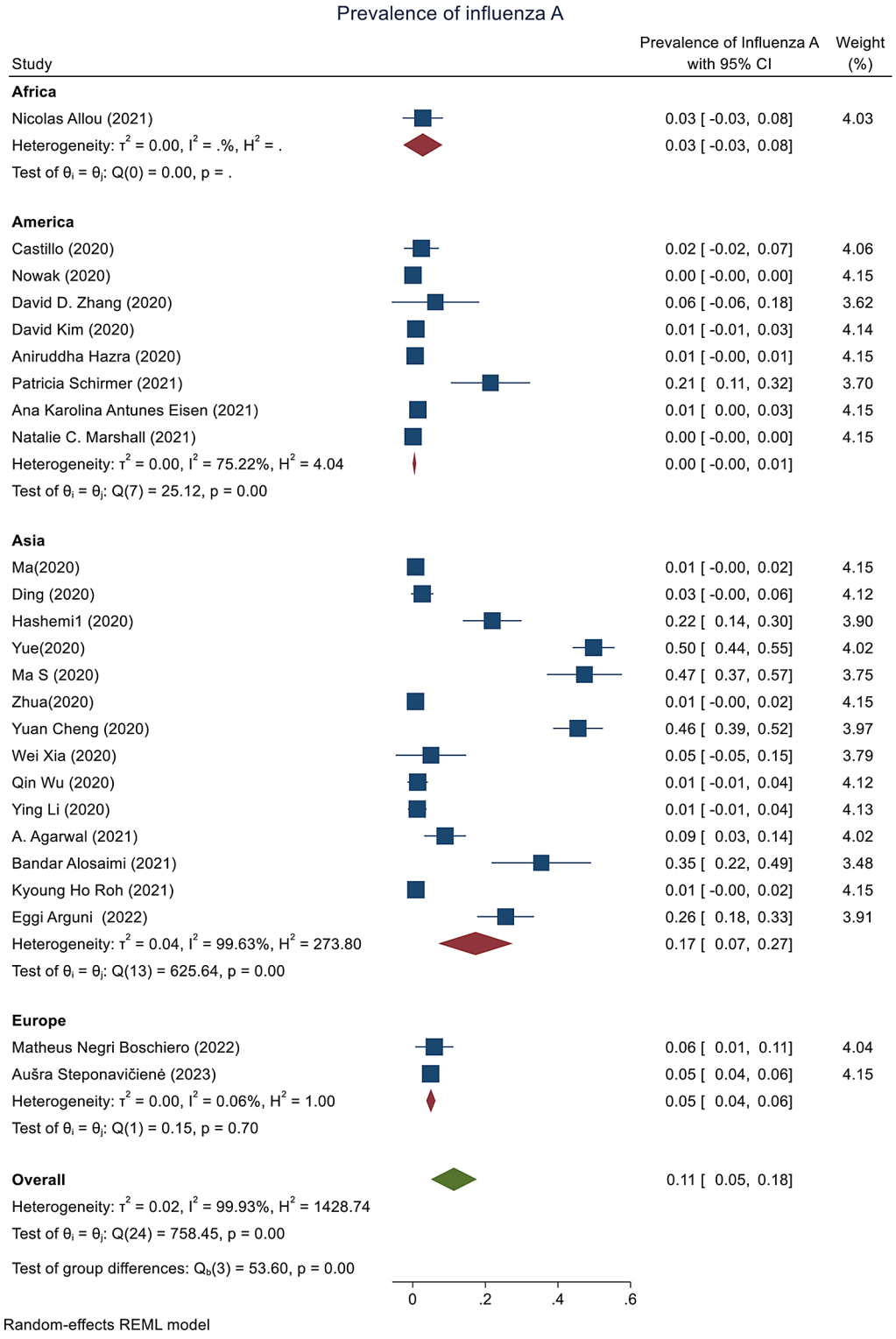

Fig. 8 Overall results of forest plot subgroup analysis for influenza A prevalence by geographic region (Asia, Africa, America and Europe)

months, the odds of being co-infected with influenza A that is actively circulating increase [48].

Other differences in the immune response that develops from infections and vaccinations can depend on reactions to past exposure to influenza viruses [49]. In some cases, individuals who have previously been exposed to influenza A, either through vaccination or past infection, may have an immune response that allows

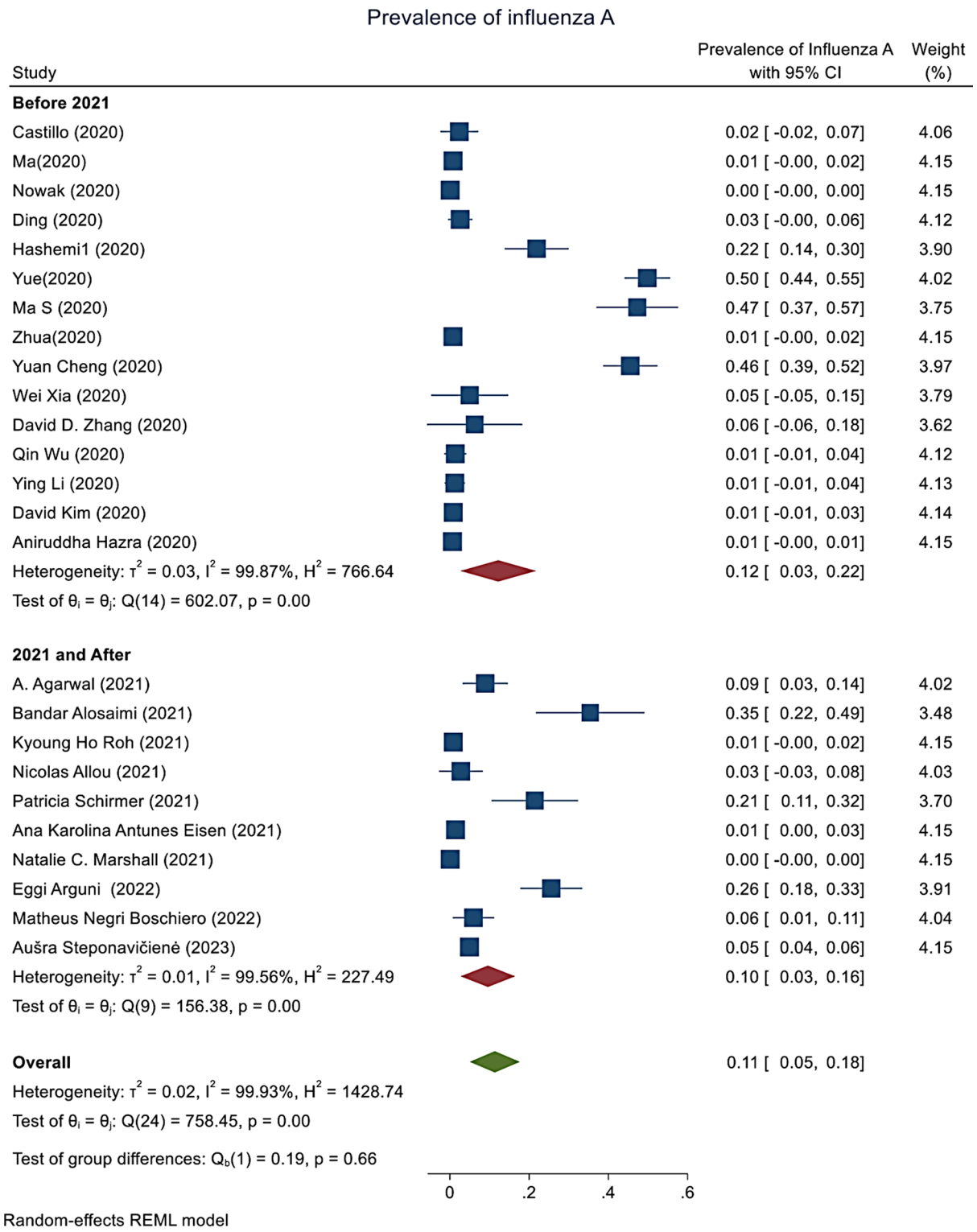

Fig. 9 Overall forest plot results for influenza A prevalence by time period (before and after 2021)

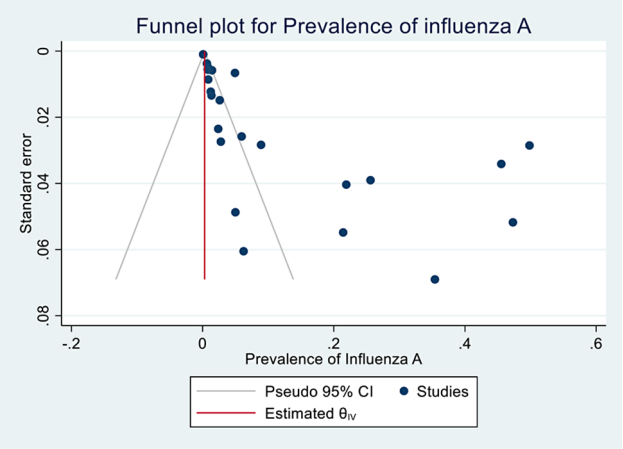

Fig. 10 Funnel plot to investigate publication bias in prevalence of influenza A in COVID-19 patients

the influenza A virus to replicate more efficiently under certain circumstances, leading to increased rates of co-infection with SARS-CoV-2. On the other hand, the response to influenza B infection may not result in the same level of concurrent infection [50].

Such as the results of this study, some clinical observations showed that both viruses can cause co-infection, but the incidence of co-infection with influenza A was slightly higher than influenza B among patients with a positive diagnosis of SARS-CoV-2, according to studies, with a higher incidence of co-infection with influenza A noted among hospitalized patients with COVID-19 due to higher transmissibility and clinical outcomes [50, 51]. Overall, according to the literature review of other studies, we ascribe the higher rate of co-infection of SARS-CoV-2 with influenza A than influenza B to the intrinsic viral properties of influenza A, epidemiological patterns during influenza A peak seasons, varying immune responses to prior exposures, and clinical observations of increased incidence of co-infections with influenza A [52].

The complexity arising from co-infection necessitates training healthcare providers (such as wearing masks and social distancing) on recognizing and managing these dual cases effectively. Standard treatment protocols for each infection may not be sufficient when both viruses are present, and therefore, individualized management strategies become crucial [53].

We can suggest some protocols for managing co-infection in COVID-19 patients, such as using accurate and reliable diagnostic tests [54]. Multiplex PCR testing is performed to simultaneously detect COVID-19 and influenza to guide appropriate therapeutic interventions [54]. Assessment of severity scoring systems for co-infected COVID-19 patients to decide whether hospitalization and support with intensive care are needed [55]. Start the eligible antiviral therapy specific to documented infections [56]. Supportive care as well as providing oxygen therapy, fluids, and supportive care, to decrease the risk of co-infections or other respiratory distress [56]. Also, high vaccination coverage against seasonal influenza and SARS-CoV-2 could reduce the risk of co-infection in recent pandemics [57, 58].

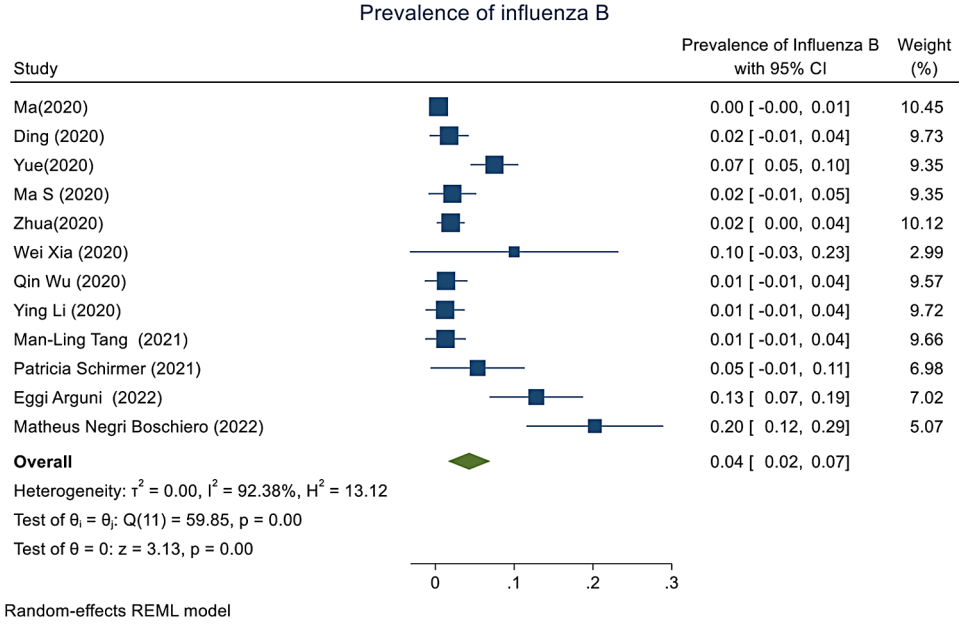

Fig. 11 Forest plot diagram for estimation of influenza B prevalence in COVID-19 patients according to each primary studies and overall estimate with a 95% confidence interval

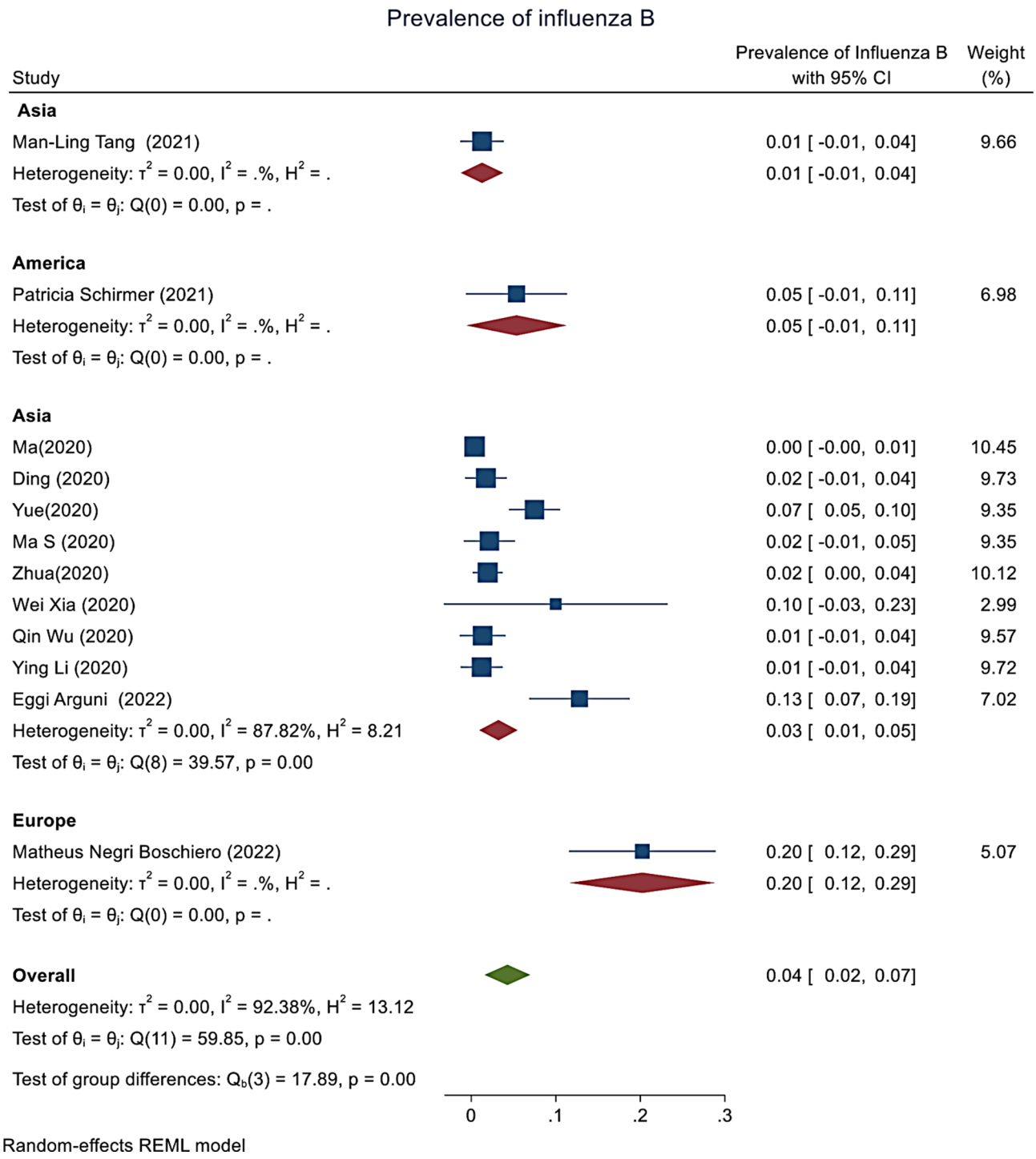

Fig. 12 Overall results of forest plot subgroup analysis for influenza B prevalence by geographic region (Asia, Africa, America and Europe)

The result of the present study shows that in the pre-2021 period, influenza prevalence was likely reduced due to strict social restrictions, but co-infection in COVID-19 patients was still significant. In contrast, in the 2021 and post-2021 periods, the easing of restrictions and wider availability of diagnostic tests may have led to increased detection of co-infections. These results suggest that despite changes in social conditions and diagnostic advances, co-occurrence prevalence has remained stable, but the high heterogeneity requires a closer examination of the sources, including further analysis to identify factors affecting differences observed across studies.

The challenge of managing patients effectively is posed by the risk of co-infection with SARS- CoV-2 and influenza,

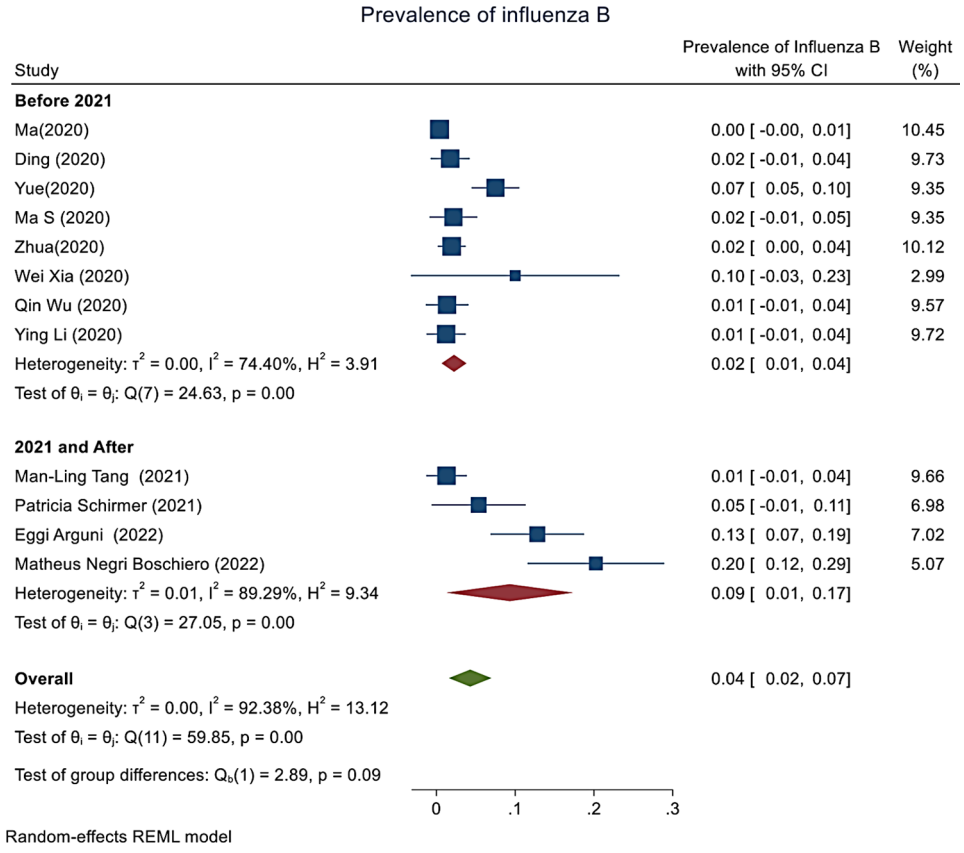

Fig. 13 Overall forest plot results for influenza B prevalence by time period (before and after 2021)

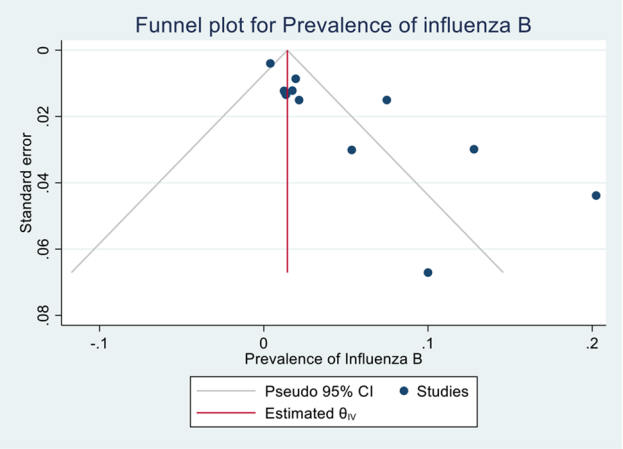

Fig. 14 Funnel plot to investigate publication bias in prevalence of influenza B in COVID-19 patients

as well as other respiratory viruses and pathogens. With co-infections, illness can be more severe and mortality rates higher, and therefore there is a need for vigilance and prevention. Overall, we must remain vigilant of the risk of co-infection with SARS-CoV-2, influenza and other respiratory pathogens when developing comprehensive public health strategies to improve patient outcomes and prevent further morbidity and mortality from these infections. The combination of SARS-CoV-2 with influenza and other respiratory viruses requires the best treatment protocols to reduce the severity of the disease. In this approach, high vaccination coverage against seasonal influenza and SARS-CoV-2 could reduce the risk of co-infection in recent pandemics. Future studies are needed for ongoing surveillance and research on the dynamics of these viral interactions in relation to public health.

Limitations

This meta-analysis has several limitations. Firstly, the number of included studies was limited, which may have impacted the precision of the estimates. Secondly, the studies included in this analysis were conducted in various countries and utilized different methods for virus detection, which may have influenced the comparability of the results.

Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS	Severe acute respiratory syndrome
MERS	Middle East respiratory syndrome
CVD	Cardiovascular disease
PRISMA-P	Systematic Review and Meta-Analyses
NOS	Newcastle–Ottawa scale
CMA	Comprehensive Meta-Analysis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10521-5.

Supplementary Material 1

Supplementary Material 2

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Author contributions
TM and RA-N performed the statistical analysis and participated in its design. MG, HJ and MR performed the literature search and collected the data. All authors read and approved the final version of the manuscript.

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Data availability
All data and materials in this article are included in the manuscript.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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Competing interests
The authors declare no competing interests.

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