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REVIEW

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Comparison of influenza type A and B with COVID-19: A global systematic review and meta-analysis on clinical, laboratory and radiographic findings

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Summary

We compared clinical symptoms, laboratory findings, radiographic signs and outcomes of COVID-19 and influenza to identify unique features. Depending on the heterogeneity test, we used either random or fixed-effect models to analyse the appropriateness of the pooled results. Overall, 540 articles included in this study; 75,164 cases of COVID-19 (157 studies), 113,818 influenza type A (251 studies) and 9266 influenza type B patients (47 studies) were included. Runny nose, dyspnoea, sore throat and rhinorrhoea were less frequent symptoms in COVID-19 cases (14%, 15%, 11.5% and 9.5%, respectively) in comparison to influenza type A (70%, 45.5%, 49% and 44.5%, respectively) and type B (74%, 33%, 38% and 49%, respectively). Most of the patients with COVID-19 had abnormal chest radiology (84%, $p < 0.001$) in comparison to influenza type A (57%, $p < 0.001$) and B (33%, $p < 0.001$). The incubation period in COVID-19 (6.4 days estimated) was longer than influenza type A (3.4 days). Likewise, the duration of hospitalization in COVID-19 patients (14 days) was longer than influenza type A (6.5 days) and influenza type B (6.7 days). Case fatality rate of hospitalized patients in COVID-19 (6.5%, $p < 0.001$), influenza type A (6%, $p < 0.001$) and influenza type B was 3%($p < 0.001$). The results showed that COVID-19 and influenza had many differences in clinical manifestations and radiographic findings. Due to the lack of effective medication or vaccine for COVID-19, timely detection of this viral infection and distinguishing from influenza are very important.

KEYWORDS
coronavirus, COVID-19, influenza, meta-analysis, SARS-Cov-2

Abbreviations: ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; CDC, Centre for Disease Controls; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reaction protein; CT scan, computed tomography scan; ESR, erythrocyte sedimentation rate; GGO, ground-glass opacity; ICU, intensive care unit; IL, interleukin; IQR, interquartile range; MCP-I, monocyte chemoattractant protein I; N, number; NA, not known; PRISMA, preferred reporting items for systematic reviews and meta-analysis statement; RT-PCR, real-time polymerase chain reaction; SARS-Cov-2, severe acute respiratory syndrome coronavirus-2; TNF-α, tumour necrosis factor-α; WBCs, white blood cells; WHO, World Health Organization.

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1 | INTRODUCTION

Influenza outbreaks are seen every year during the colder months of the year. Until now, four influenza pandemics have been reported, including the H1N1 (1918), the H2N2 (1957), the H3N2 (1967) and the H1N1 pandemic in 2009.[1] In addition, seasonal flu is reporting in different countries every year. Influenza mortality is associated with age, underlying disease and pregnancy.[2,3] The most important clinical findings in patients with influenza are fever, cough and runny nose.[4,5] According to the Centre for Disease Controls (CDC), the influenza virus has infected 35.5 million people, with 490,600 people hospitalized and about 34,200 have died in the United States between 2018 and 2019. The influenza virus is divided into four types (A, B, C and D) by antigenic differences in their core proteins, including matrix protein (M1) and nucleoprotein (NP).[6] Types A and B are the dominant types of circulating influenza virus, and the most influenza epidemics are related to type A. Influenza type A viruses are subdivided into subtypes according to glycoproteins on the surface of the virus: hemagglutinin (HA) and neuraminidase (NA). There are 18 different HA subtypes and 11 different NA subtypes (H1–H18 and N1–N11, respectively).[6] Current subtypes of influenza A viruses that routinely circulate in people include flu A (H1N1) and A (H3N2)[6]. Type A subtypes often cause mild and symptomatic respiratory illness, but some subtypes such as H5N1 are highly pathogenic and have a higher mortality rate.[6]

In the last 20 years, in addition to the influenza virus, other respiratory viruses belonging to coronavirus families such as severe acute respiratory syndrome (SARS) (in 2002) and Middle East respiratory syndrome (in 2012) were among the most severe respiratory pathogens.[6] In late 2019, the SARS-Cov-2 virus caused the COVID-19 infection, and it became a pandemic disease in a short time. Between December 2019 and 26 April 2020, about three million people were infected with COVID-19, and about 300,000 died from the disease. Both influenza and SARS-Cov-2 viruses cause respiratory disease with a wide range of asymptomatic or mild to severe disease.[7] Also, both viruses are transmitted via contact, droplets and contaminated surfaces.[8] Moreover, basic reproduction number R zero (R0) for COVID–19 (1.5–5.7) is more significant than influenza (0.9–2.1), which shows that the SARS-Cov-2 virus can infect more people than influenza.[8–12]

Children are the primary group of virus carriers in influenza infections.[13] Moreover, children, older adults, pregnant women, individuals with underlying chronic disease and immunosuppressed patients are at high risk of severe influenza infection.[13–15] While, in the COVID-19, children are less affected than adults and the older age with underlying conditions, and are associated with severe symptoms of the disease.[16] Among COVID-19 patients, the primary treatment is mostly supportive, although multiple experimental antiviral medications are being evaluated.[17,18] Thus, prevention and rapid diagnosis of infected patients are crucial. Most of the clinical symptoms of COVID-19 patients are similar to influenza infections. Therefore, in this study, we attempted to distinguish the clinical symptoms, laboratory findings, radiographic signs and outcomes of confirmed COVID-19 and influenza patients. All findings are compared to determine the unique features among each virus. These data could be helpful in the early diagnosis and prevention of infection as well as providing more reliable epidemiological data on a large scale for healthcare policies and future studies.

2 | METHODS

2.1 | Search strategy

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) guidelines.[19] We searched all studies published up to 26 April 2020, from the following databases: Embase, Scopus, PubMed, Web of Science and the Cochrane library. Search medical subject headings (MeSH) terms used were 'COVID-19', 'SARS Cov-2', 'severe acute respiratory syndrome coronavirus 2', 'coronavirus disease 2019 virus', '2019 novel coronavirus', 'COVID-19 virus', 'influenza virus,' 'influenza,' 'Human flu', and all their synonyms like 'SARS-CoV-2' and '2019-nCoV'. Moreover, we searched for unpublished and grey literature with Google scholar, CDC and World Health Organization (WHO) databases. We also examined references of included articles to find additional relevant studies. There was no language restriction, and all included studies were written in English or Chinese languages; the letter was translated by https://translate.google.com/. Additional search strategy details are provided in Table S1.

2.2 | Study selection

Duplicate studies were removed using EndNote X7 (Thomson Reuters). Records were initially reviewed by title and abstract by independent five authors (AP, SG, MR, AK and EA). The full text of potentially eligible records was retrieved and examined, and any disagreement was resolved by consensus.

2.3 | Eligibility and inclusion criteria

Studies to be eligible for inclusion in our meta-analysis had to have following pre-determined criteria. All case-control, cross-sectional, cohort studies, case reports and case series peer-reviewed studies were included if they reported the number of confirmed cases of patients with demographic data [AND] [OR] clinical data [AND] [OR] radiology data [AND] [OR] laboratory data [AND] [OR] risk factor data. Also, influenza virus studies from 2000 to 2020 were included.

2.4 | Exclusion criteria

Studies without the number of confirmed cases, letters to editor, review articles, individual case reports and news reports were excluded. Duplicate data from the same patients were combined and counted as a single case when the data were reported more than one.

2.5 | Data extraction

All COVID-19 included literature that was published in 2020, and all influenza studies were from 2000 to 2020. The following items were extracted from each article: first author, centre and study location, countries, sample collection time, patient follow-up time, the reference standard for infection confirmation, number of confirmed cases, study type, and all demographic, clinical, radiological, laboratory data and risk factor data. Four of our authors (Saied Ghorbani, Mohammad Hossein Razizadeh, Ehsan Alborzi and Alireza Khatami) independently extracted data, and all extracted data were checked randomly by another author (Ali Pormohammad); the differences were resolved by consensus.

2.6 | Quality assessment

Quality assessments of studies were performed by two reviewers independently according to the critical appraisal checklist recommended by the Joanna Briggs Institute, and disagreements were resolved by consensus. The checklist is composed of nine questions that reviewers addressed for each study. The 'Yes' answer to each question received one point. Thus, the final scores for each study could range from 0 to 9 (Table S2).

2.7 | Analysis

Data cleaning and preparation were done in Microsoft Excel 2010 (Microsoft©), and further analyses were carried out via Comprehensive Meta-Analysis Software Version 2.0 (Biostat). Determination of heterogeneity among the studies was undertaken using the chi-squared test (Cochran's Q) to assess the appropriateness of pooling data. Depending on the heterogeneity test, we used either random- or fixed-effect model for pooled results. In the case of high heterogeneity (I^2 >50%), a random-effect model (M-H heterogeneity) was applied, while in low heterogeneity cases (I^2 < 50%), a fixed-effect model was used.[20] Percentages and means ± SDs were calculated to describe the distributions of categorical and continuous variables, respectively. *p*-Values reflect study heterogeneity with <0.05 being significant. We also used the funnel plot, Begg's and Egger's tests based on the symmetry assumption to detect publication bias (Figure S1).

3 | RESULTS

3.1 | Characteristics of included studies

The process of study selection is represented in Figure 1. A total of 194,092 reports were screened for the analysis of patients with COVID-19 and influenza; 363,827 of them were excluded after the duplicate removing, title and abstract screening, and the full text of 611 reports were reviewed in full text. We excluded studies that did not report sufficient data. Out of 540 included studies, 157 studies met the inclusion criteria for COVID-19 and 383 for influenza. The characteristics of the selected articles are summarized in Table S5. Of the 157 COVID-19 studies that were included in the analysis, 155 studies were in English and 2 of them were in Chinese languages.[21,22] All COVID-19 studies were retrospective, published in 2020, and 150 studies were from China, 2 from the United States, 1 from Italy, 1 from Japan, 1 from the United Kingdom, 1 from Iran and 1 from Taiwan. All influenza studies were from 2000 to 2020, and out of 383 influenza studies, 251 studies were influenza A and 47 studies were influenza B.

3.2 | Quality assessment

Quality assessment of included studies was performed based on the critical appraisal checklist, and the final quality scores of the included studies are represented in Table S2. In brief, studies by Chen,[23] Wang,[24] Huang,[25] Guan,[26] Zhang,[27] Cheng,[28] Li,[29] Wei Xu[30] and Song[31] had the highest quality of the COVID-19 studies available to date in the purpose of this study.

3.3 | Demographics, baseline characteristics and clinical characterization

Overall, 75,164 confirmed patients with COVID-19 infection, 113,818 with influenza type A and 9266 with influenza type B were included in the meta-analysis, of which 51% (95% CI 50–52.2, $p < 0.001$) of COVID-19, 54% (95% CI 53–54.5, $p < 0.001$) of influenza type A and 52% (95% CI 48–55.5, $p < 0.001$) of influenza type B included patients who were male. Funnel plots for included studies did not detect significant publication bias (Figure S1). Table 1 shows that most patients of COVID-19 (76% [95% CI 72.5–79, $p < 0.001$]), influenza type A (87.5% [95% CI 85–90, $p < 0.001$]) and influenza type B (89.5% [95% CI 83–93, $p < 0.001$]) had fever. Cough was the second most common symptom presenting in the patients of COVID-19 (54% [95% CI 50–58, $p < 0.001$]), influenza type A (83.5% [95% CI 81–85, $p < 0.001$]) and influenza type B (79% [95% CI 75–84, $p < 0.001$]). Runny nose was the third most common symptom presenting in the patients of influenza type A (70% [95% CI 71–72, $p < 0.001$]) and influenza type B (74% (95% CI 72–75, $p < 0.001$]) of patients. While runny

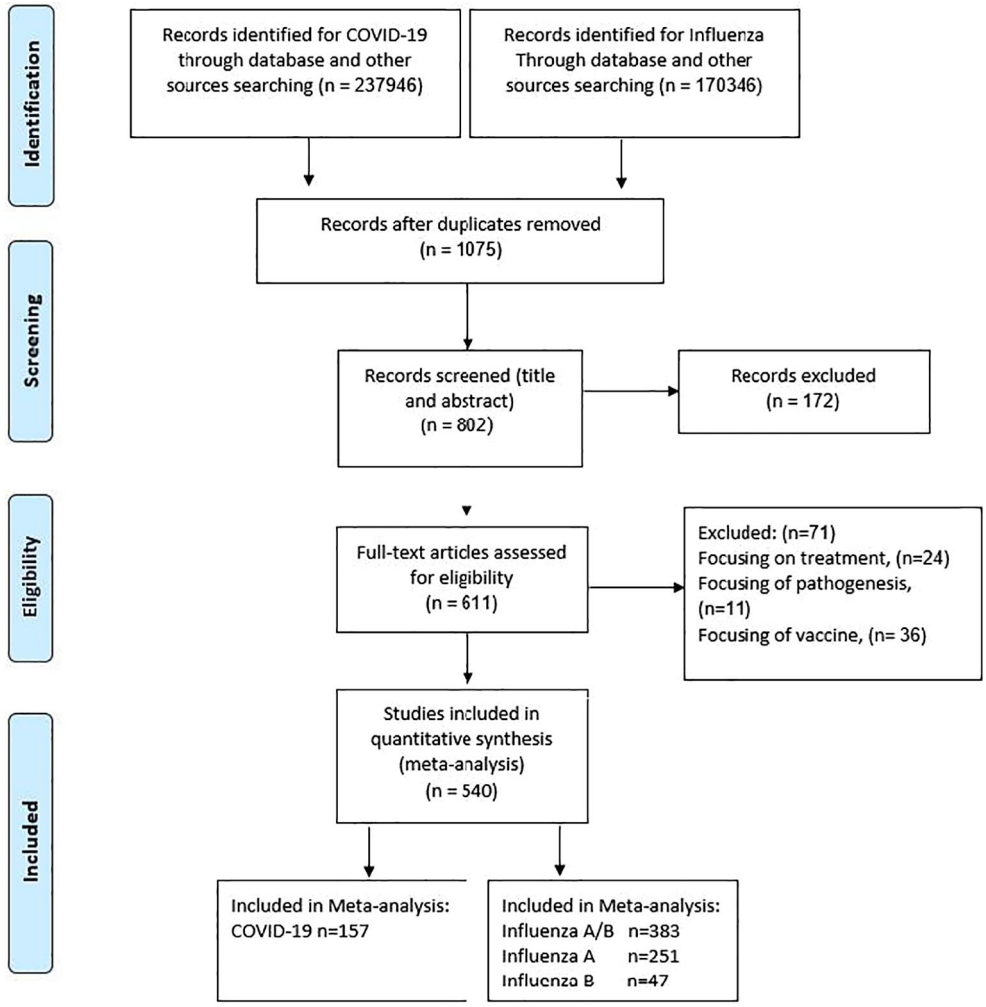


FIGURE 1 Flow diagram of literature search and study selection (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement [PRISMA] flow chart)

nose was less common symptom in COVID-19 and it is presented in 14% (95% CI 7.3–25, $p < 0.001$) of patients. Also, fatigue was the fourth most common symptom in influenza type A (60% [95% CI 59–61, $p < 0.001$]), while it was less common in COVID-19 (27% [95% CI 23–31.5, $p < 0.001$]) and influenza type B (21% [95% CI 18–24, $p < 0.001$]) patients. Dyspnea was less common in COVID-19 patients (15% [95% CI 12–19, $p < 0.001$]), in comparison to influenza type A (45.5% [95% CI 41–50, $p < 0.001$]) and influenza type B (33% [95% CI 23.5–45, $p < 0.001$]). Likewise, sore throat was less common in COVID-19 patients (11.5% [95% CI 9–14, $p < 0.001$]), in comparison to influenza type A (49% [95% CI 48–51, $p < 0.001$]) and influenza type B (38% [95% CI 36–39, $p < 0.001$]). Also, rhinorrhea was less common in COVID-19 patients (9.3% [95% CI 6–14, $p < 0.001$]), in comparison to influenza type A (44.5% [95% CI 39–49.5, $p < 0.001$]) and influenza type B (49% [95% CI 42–56, $p < 0.001$]). There was no information about coryza in COVID-19 patients, while it is presented in influenza type A by 47% (95% CI 43–52, $p < 0.001$) and influenza type B by 32% (95% CI 10–67, $p < 0.001$) of the patients (Figure 2).

3.4 | Risk factors and common comorbid of patients infected with COVID-19

Up to 26 April 2020, 51% (95% CI 44–58, $p < 0.001$) of COVID-19 patients had a history of recent travel or contact with endemic people, and 43.5% (95% CI 35–52, $p < 0.001$) had contacted with another person with respiratory symptoms. Another risk factor for COVID-19 was healthcare worker by 23% (95% CI 10–43, $p < 0.001$). The most common comorbid chronic condition for COVID-19 and influenza type A is hypertension by 20% (95% CI 16–25, $p < 0.001$) and diabetes for influenza type B by 19% (95% CI 11–29, $p < 0.001$). Acute respiratory syndrome (ARDS) occurred more frequently presented in influenza type A by 31.5% (95% CI 26–38, $p < 0.001$) compared to COVID–19 by 26.6% (95% CI 18–38, $p < 0.001$) and influenza type B by 0.8% (95% CI 0.1–6, $p < 0.001$). Virus co-infection occurred more frequently in influenza type B by 24% (95% CI 8–54, $p < 0.001$), in comparison to influenza type A by 8.5% (95% CI 5.5–13, $p < 0.001$) and COVID–19 by 4% (95% CI 1.5–10, $p < 0.001$) patients (Figure 3).

TABLE 1 Meta-analysis on demographics, baseline characteristics and clinical outcomes of patients with confirmed COVID-19, influenza type A and influenza type B

	COVID-19 (total of 157 studies, 75,164 patients)					Influenza type A (total 251 studies, 113,818 patients)					Influenza type B (total 47 studies, 9266 patients)				
	Clinical presentation* (CI 95%)	Included studies number	Included patients number	*I*-squared**	*p*-value**	Clinical presentation* (CI 95%)	Included studies number	Included patients number	*I*-squared**	*p*-value**	Clinical presentation* (CI 95%)	Included studies number	Included patients number	*I*-squared**	*p*-value**
Age, years	49.7 (mean) (43–54)	123	24,360	99	<0.001	36.5 (26–48)	164	64,602	99	<0.001	38.5 (32–42)	27	4179	99	<0.001
Sex (male)	51 (50–52.2)	144	71,778	72.5	<0.001	54 (53–54.5)	212	98,403	81	<0.001	52 (48–55.5)	28	4513	77	<0.001
Fever	76 (72.5–79)	113	15,537	94	<0.001	87.5 (85–90)	171	61,212	97	<0.001	89.5 (83–93)	31	8388	97	<0.001
Cough	54 (50–58)	114	15,162	93	<0.001	83.5 (81–85)	164	59,840	96	<0.001	79 (75–84)	26	7735	94	<0.001
Fatigue	27 (23–31.5)	82	12,645	94	<0.001	60 (59–61)	40	13,637	96	<0.001	21 (18–24)	6	750	86	<0.001
Sputum production	21 (18–24)	42	4506	81	<0.001	34 (33.5–35)	56	22,107	96	<0.001	26 (23–27)	6	4546	97	<0.001
Myalgia	20 (16–24)	41	5077	87	<0.001	32 (27–36)	90	39,018	98	<0.001	22.5 (11–40)	15	6397	98	<0.001
Dyspnoea	15 (12–19)	51	7761	93	<0.001	45.5 (41–50)	105	34,079	98	<0.001	33 (23.5–45)	9	973	90	<0.001
Chill	14 (9–21)	18	2577	91	<0.001	34 (28–40)	36	25,479	98	<0.001	25.5 (12–26)	7	4706	98	<0.001
Sore throat	11.5 (9–14)	46	7737	82	<0.001	49 (48–51)	116	47,041	96	<0.001	38 (36–39)	20	6475	95	<0.001
Headache	10.5 (9–12)	59	9311	75	<0.001	28 (18–30)	96	36,580	99	<0.001	13.4 (8.5–20)	14	3643	95	<0.001
Chest pain	10.5 (8–13.5)	41	6759	91	<0.001	9 (7–12)	41	1,6670	95	<0.001	11 (6–20)	7	1245	89	<0.001
Diarrhoea	8.5 (6.6–11)	78	11,421	91	<0.001	12 (10–14)	112	27,360	94	<0.001	9 (5.5–15)	16	3942	96	<0.001
Rhinorrhoea	9.3 (6–14)	16	879	60	0.001	44.5 (39–49.5)	70	29,166	98	<0.001	49 (42–56)	17	2190	89	<0.001
Nausea and vomiting	6 (4–8)	36	5063	86	<0.001	20 (17–22.5)	107	28,728	96	<0.001	20 (16–26)	18	3872	91	<0.001
Runny nose	14 (7.3–25)	14	1758	91	<0.001	70 (71–72)	19	12,814	97	<0.001	74 (72–75)	4	3618	96	<0.001
Pneumonia	NA	NA	NA	NA	NA	28 (24–34)	94	43,192	98	<0.001	14.5 (10–20)	23	4571	93	<0.001
Croup	NA	NA	NA	NA	NA	4 (2–5)	13	6712	84	<0.001	4 (2–4.5)	6	2120	0	0.4
Coryza	NA	NA	NA	NA	NA	47 (43–52)	16	6819	88	<0.001	32 (10–67)	3	1857	98	<0.001
Asthma	NA	NA	NA	NA	NA	12 (10–14)	89	61,655	96	<0.001	15 (7–29)	4	570	88	<0.001

(Continues)

TABLE 1 (Continued)

Comorbid conditions	COVID-19					Influenza type A					Influenza type B				
	Clinical presentation* (CI 95%)	Included studies number	Included patients number	*I*-squared**	*p*-value**	Clinical presentation* (CI 95%)	Included studies number	Included patients number	*I*-squared**	*p*-value**	Clinical presentation* (CI 95%)	Included studies number	Included patients number	*I*-squared**	*p*-value**
Travel history[a]	51 (44–58)	52 7	54,154	98	<0.001	–	–	–	–	–	–	–	–	–	–
Contact history[b]	43.5 (35–52)	48	7126	96	<0.001	–	–	–	–	–	–	–	–	–	–
Hypertension	20 (16–25)	66	54,151	97	<0.001	20 (16–25)	42	15,915	96	<0.001	7 (4–12)	1	194	0	1
ARDS	26.6 (18–38)	5	3826	95	<0.001	31.5 (26–38)	51	17,762	96	<0.001	0.8 (0.1–6)	1	55	0	1
Diabetes	10.5 (7.5–14.5)	61	46,232	97	<0.001	11 (10–13)	107	66,761	94	<0.001	19 (11–29)	6	850	88	<0.001
Current smoker	10.5 (6.5–16)	28	6643	96	<0.001	20 (16–24)	53	20,914	92	<0.001	14 (10–20)	4	395	22	0.3
Chronic liver disease	5.4 (4–7)	34	5269	79	<0.001	3 (2–4.5)	55	53,532	97	<0.001	2 (7–6.5)	5	1920	85dia	<0.001
Digestive system disease	6 (4–10)	28	5807	93	<0.001	15 (13–18)	39	22,105	95	<0.001	15 (10–20)	10	4463	86	<0.001
Healthcare worker	23 (10–43)	10	46,509	95	<0.001	4 (105–10)	8	3753	97	<0.001	NA	NA	NA	NA	NA
Past smoker	6.5 (5–9)	5	1307	33	0.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cardiovascular and cerebrovascular diseases	10.5 (7–15)	56	54,270	98	<0.001	9.5 (8–11)	134	72,509	96	<0.001	9 (3.5–20)	8	2407	95	<0.001
Chronic respiratory disease	9.5 (6–14)	33	49,731	95	<0.001	12 (10–12)	112	67,817	96	<0.001	16 (10–24)	8	988	85	<0.001
Nervous system disease	3 (0.1–6)	2	314	92	<0.001	7 (6–9)	90	63,704	97	<0.001	3 (2–7)	12	2614	2614	87
HIV	2 (0.2–14)	2	232	70	0.06	3.5 (2.5–4.5)	13	26,637	85	<0.001	NA	NA	NA	NA	NA
Cancer	3 (2–5)	41	52,749	93	<0.001	7 (5.5–8.5)	52	39,954	93	<0.001	10 (5–18)	6	850	85	<0.001
Renal failure	7 (4–11)	39	5676	91	<0.001	5 (4–6)	9	64,775	95	<0.001	7 (2–17)	8	1077	94	<0.001
Bacteria co-infection	4.5 (1.5–12)	10	1196	84	<0.001	12 (9–15)	62	14,326	85	<0.001	15 (7–29)	9	740	83	<0.001
Fungi co-infection	4.8 (2–11)	2	109	0	0.4	1.5 (1–2)	9	3580	38	0.1	20 (6–42)	3	95	74	0.03
Virus co-infection	4 (1.5–10)	10	2499	88	<0.001	8.5 (5.5–13)	47	33,680	97	<0.001	24 (8–54)	10	2027	96	<0.001

TABLE 1 (Continued)

Chest x-ray and CT scan findings															
	COVID-19					Influenza type A					Influenza type B				
	Clinical presentation* (CI 95%)	Included studies number	Included patients number	*I*-squared**	*p*-value**	Clinical presentation* (CI 95%)	Included studies number	Included patients number	*I*-squared**	*p*-value**	Clinical presentation* (CI 95%)	Included studies number	Included patients number	*I*-squared**	*p*-value**
Abnormal chest x-ray	84 (78–8.5)	12	1706	85	<0.001	57 (50–64)	65	19,500	89	<0.001	33 (6–80)	5	651	86	<0.001
Bilateral involvement	76.8 (62.5–87)	12	46,270	94	<0.001	37.5 (27.5–48.5)	35	6003	88	<0.001	16.5 (7–35)	4	545	87	<0.001
Consolidation	75.5 (50.5–91)	6	1378	92	<0.001	27 (17–40)	25	8730	98	<0.001	27.5 (8–62)	3	95	78	0.09
Ground-glass opacity	71 (40–90)	12	46,270	87	<0.001	47 (30–65)	7	529	90	<0.001	6.5 (0.3–65)	2	73	80	<0.001
Unilateral involvement of chest radiography	15.5 (10.5–22.5)	29	4615	94	<0.001	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Outcome															
	COVID-19					Influenza type A					Influenza type B				
	Clinical presentation* (CI 95%)	Included studies number	Included patients number	*I*-squared**	*p*-value**	Clinical presentation* (CI 95%)	Included studies number	Included patients number	*I*-squared**	*p*-value**	Clinical presentation* (CI 95%)	Included studies number	Included patients number	*I*-squared**	*p*-value**
Incubation period (mean) (day)	6.4 (5.8–7)	53	12,609	98	<0.001	3.4 (2.25–4.5)	8	784	97	<0.001	NA	NA	NA	NA	NA
Discharged	57.5 (49.5–62.5)	57	7906	96	<0.001	82 (77–86)	122	68,373	98	<0.001	87.5 (63–97)	14	2646	97	<0.001
Duration of hospitalization (mean) (day)	14 (12–16)	32	3674	97	<0.001	6.5 (6–8)	82	23,510	98	<0.001	6.7 (5.3–8)	15	2227	97	<0.001
Mortality	6.2 (6–6.5)	64	56,269	97	<0.001	6 (5–6.5	133	78,648	97	<0.001	3 (2–4)	13	2912	85	<0.001

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; CT scan, computed tomography scan; ICU, intensive care unit; NA, not available.

[a]Recent travel or contact with endemic people resident of Wuhan.

[b]Contact with another person with respiratory symptoms.

*Age is an exception, presented in mean age in years.

**Greater than 50% is considered high heterogeneity, less than 50% is considered low heterogeneity. A low *p*-value (<0.05) is consistent with high heterogeneity.

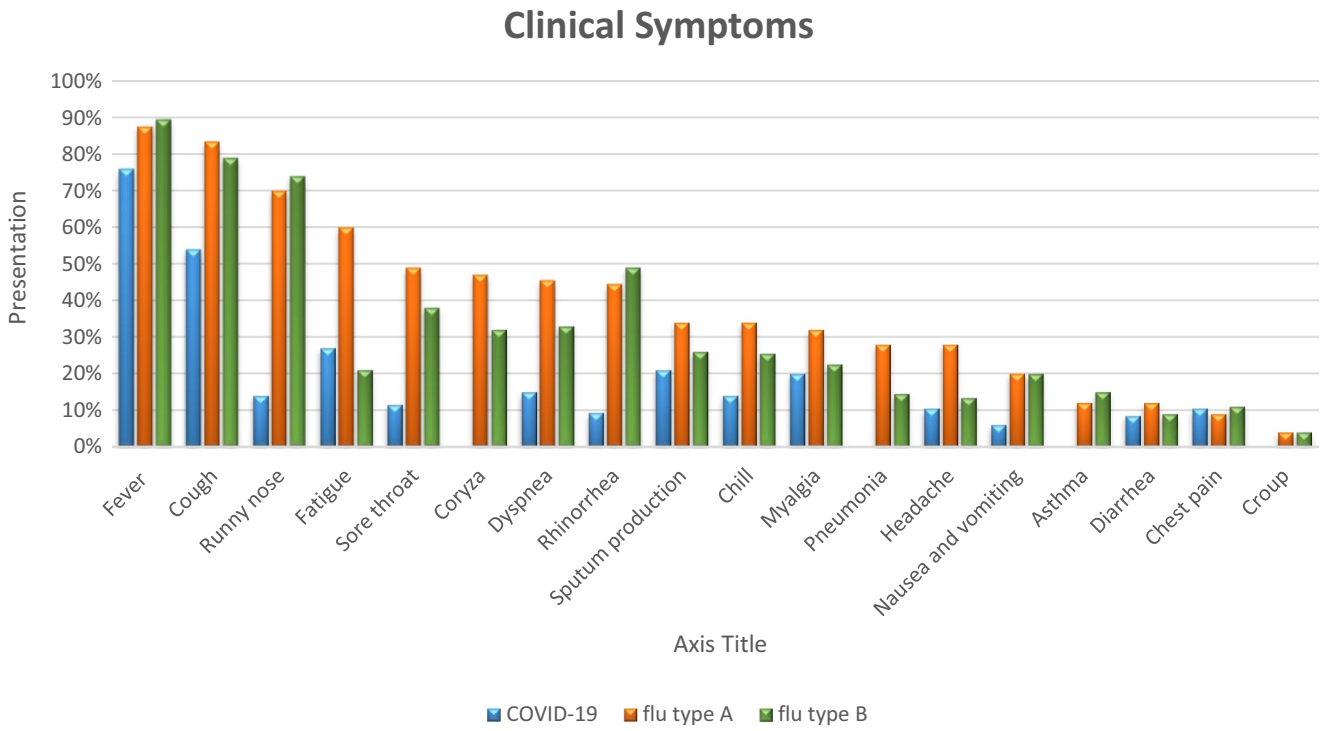


FIGURE 2 Meta-analysis on symptoms presentation of patients with confirmed COVID-19, influenza type A and influenza type B

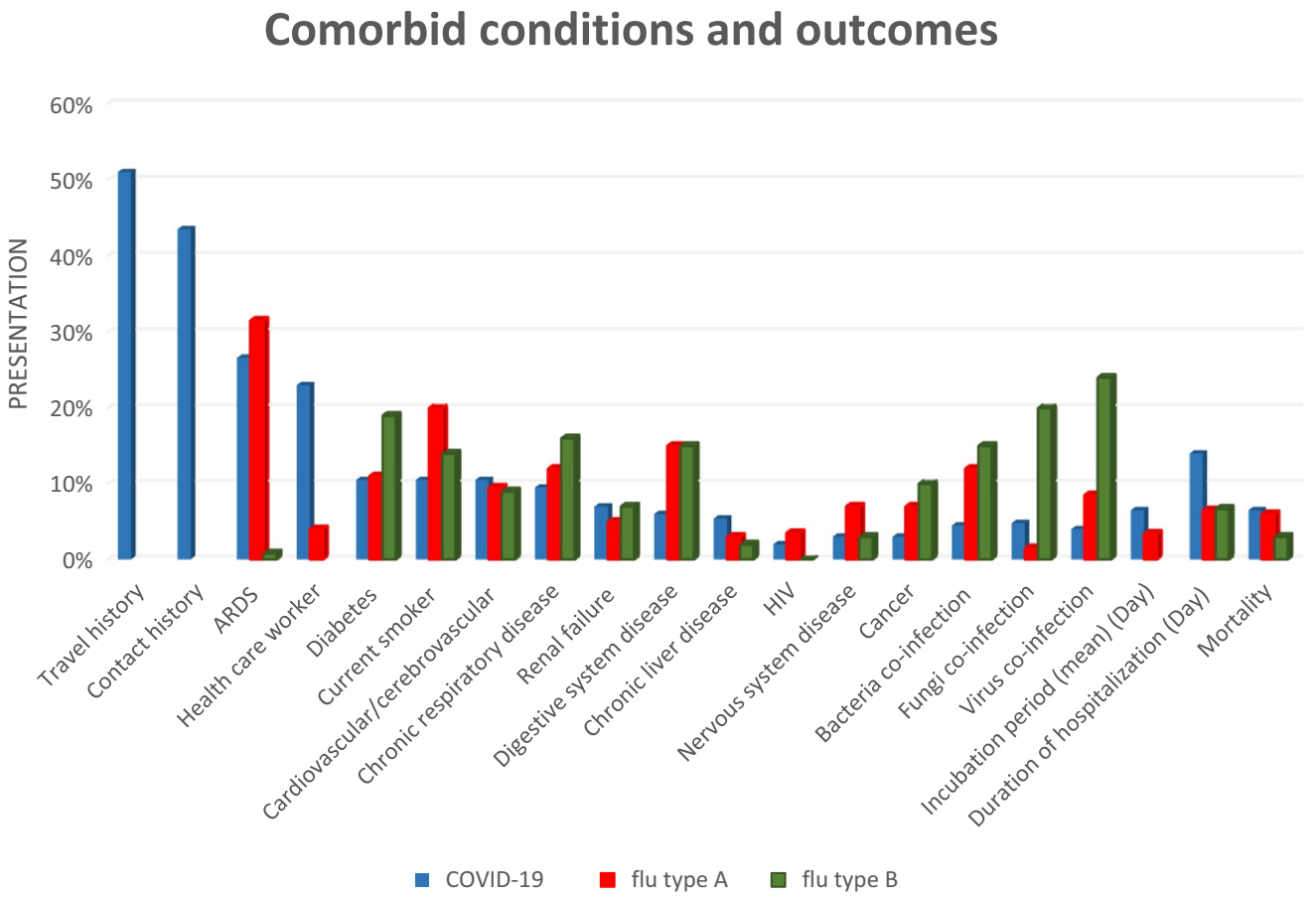


FIGURE 3 Meta-analysis on presentation of comorbid conditions and outcomes of patients with confirmed COVID-19, influenza type A, and influenza type B. ARDS, acute respiratory distress syndrome

TABLE 2 Meta-analysis: mortality rate of COVID-19 patients in different age ranges

Age groups (year)	Mortality rate (%) (CI 95%)	Included studies number	Included patients number	Heterogeneity test, *I*-squared (%)**	Heterogeneity test, *p*-value**
<8	0.6 (0–9)	1	82	0	1
>50	38 (35–40)	14	1935	85	<0.001
All range	4.3 (4–4.5)	49	54,252	92	<0.001
Overall	6.2 (6–6.5)	64	56,269	91	<0.001

3.5 | Chest x-ray and CT scan findings in patients infected with COVID–19

Analysis showed that 84% (95% CI 78–8.5, $p < 0.001$) of COVID–19 patients, 57% (95% 50–64, $p < 0.001$) of influenza type A patients and 33% (95% 6–80, $p < 0.001$) of influenza type B patients had abnormal radiological findings on chest x-ray and CT scans. The most common radiological abnormalities in COVID–19 patients were bilateral involvement of chest x-ray by 76.8% (95% CI 62.5–87, $p < 0.001$), consolidation by 75.5% (95% CI 50.5–91, $p < 0.001$) and ground-glass opacity (GGO) by 71% (95% CI 40–90, $p < 0.001$) (Table 1).

3.6 | Outcome

Based on the available data, the mean incubation period was 6.4 days (95% CI 5.8–7, $p < 0.001$) in 12,609 COVID-19 cases and 3.4 days (95% CI 2.25–4.5, $p < 0.001$) in 784 influenza type A, while there is no available data about the incubation period of influenza type B in the included articles. The mean duration of hospitalization among 3674 COVID-19 confirmed cases was 14 days (95% CI 12–16, $p < 0.001$), 6.5 days (95% CI 6–8, $p < 0.001$) in 23,510 influenza type A cases and 6.7 days (95% CI 5.3–8, $p < 0.001$) in 2227 influenza type B cases . The hospital discharged rate of COVID–19 was 57.5% (95% CI 49.5–62.5, $p < 0.001$), which was lower in comparison to influenza type A (82% [95% CI 77–86, $p < 0.001$]) and influenza type B (87.5% [95% CI 63–97, $p < 0.001$]) patients.

Case fatality rate of COVID-19 hospitalized patients was 6.5% (95% CI 4.5–9, $p < 0.001$) (Figure S2), influenza type A was 6% (95% 5–6.5, $p < 0.001$) and influenza type B was 3% (95% CI 2–4, $p < 0.001$).

3.7 | The influenza mortality rate in different subtypes and countries

The mortality rate in the influenza A subtypes are subtypes H1N1 (5.5% [95% CI 4–7, $p < 0.001$]), H3N2 (1.7% [95% CI 0.2–15, $p < 0.001$]), H5N1 (42% [95% CI 29–56, $p < 0.001$]), H7N9 (30% [95% CI 25.6–35, $p < 0.001$]) and non-H1N1 (2% [95% CI 1–5, $p < 0.001$]). Influenza mortality rate was associated with age, and the high mortality rate was in ≥50-year-old ages (12% [95% CI 6–22.5, $p < 0.001$]) (Table 2). Influenza H1N1 mortality rate in ICU cases was 25% (95% CI 15.5–37.6, $p < 0.001$) (Figure 4).

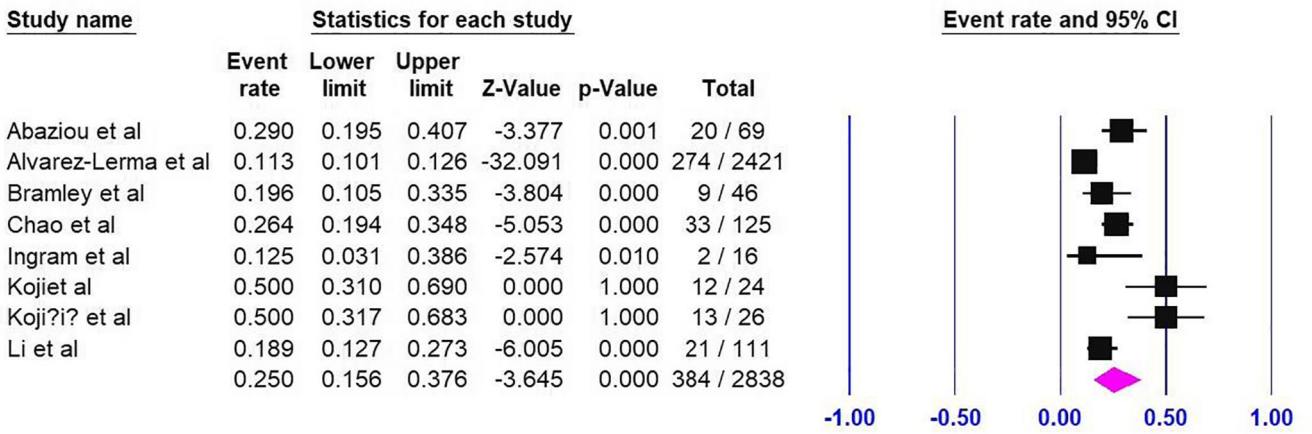
Figure 5 showed influenza type A, B and A/B mortality rates in different countries based on the reported data from these countries. The highest mortality by influenza type A/B was reported in Indonesia at 77% (95% 48–92, p 0.9) and the lowest mortality rate in Rwanda at 0.1% (95% CI 0–1.5, p 0.9) (Table S3). Vietnam had the highest mortality in influenza type A by 33% (95% CI 20–48, $p < 0.17$), and Kuwait had the lowest mortality rate by 0.4% (95% CI 0.1–2.5, p 0.9) (Table S4). Moreover, Spain had the highest mortality in influenza type B by 12.5% (95% CI 0.7–73, $p < 0.9$), and France had the lowest mortality rate by 0.9% (95% CI 0.6–1.5, p 0.9) (Figure S3).

3.8 | Laboratory findings of patients infected with COVID-19

The laboratory findings showed that among 10,185 COVID-19 cases where data were available, lymphopenia was 62.5% (95% CI 45–72, $p < 0.001$), which is more than influenza type A (8820 cases) at 49% (95% CI 35–56.4, $p < 0.001$) (Table 3). In addition, C-reactive protein increased in 1054 COVID-19 patients by 81% (95% CI 68–89, $p < 0.001$), in 5237 influenza type A patients by 62% (95% CI 55–73, $p < 0.001$), and in 287 influenza type B patients by 43% (95% CI 37–49, $p < 0.001$). In COVID-19 confirmed patients, 80% (95% CI 75–85, $p < 0.001$) had decreased albumin and 1783 patients had increased LDH at 70.3% (95% CI 65–76, $p < 0.001$) (Table 4).

4 | DISCUSSION

Influenza and coronavirus are associated with respiratory diseases, which in most cases are asymptomatic, and the symptoms in patients can range from mild to severe disease and death.[32] After the influenza epidemic in 2017–2019, COVID-19 reported as a contagious respiratory illness. The diagnosis of these viruses is essential. However, distinguishing these two viruses is challenging due to similar clinical signs and the same way of transmission. Our results show that fever and cough were the most common clinical symptoms in COVID-19, influenza type A and influenza type B. In addition, runny nose was the third most common clinical finding among influenza A/B patients, while it was less common among COVID-19. Among 75,164 patients



Model	Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	8	0.142	0.129	0.156	-32.216	0.000	86.085	7	0.000	91.868	0.601	0.515	0.265	0.775
Random	8	0.250	0.156	0.376	-3.645	0.000								

FIGURE 4 Meta-analysis forest plot on mortality rate of influenza type A (subtype H1N1) in intensive care unit. All patients in two Kojiret studies (from Bosnia and Herzegovina) were mechanically ventilated patients

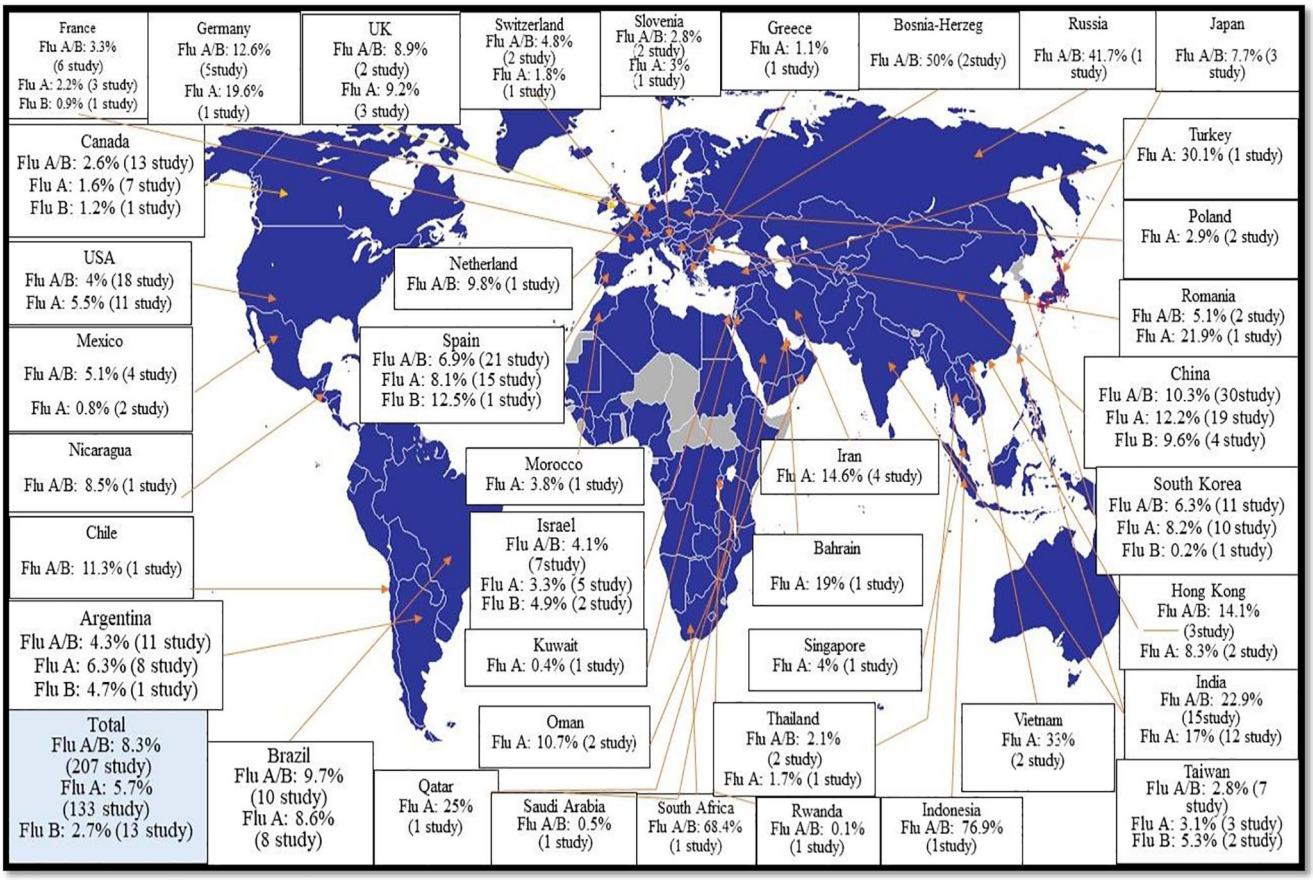


FIGURE 5 Meta-analysis; global estimate of influenza type A, B and A/B hospitalized patients' case fatality rate (all patients in two Bosnia and Herzegovina studies were mechanically ventilated patients)

TABLE 3 Meta-analysis; mortality rate of influenza type and subtypes in different age ranges

	Age groups (year)	Mortality rate (%) (CI 95%)	Included studies number	Included patients number	Heterogeneity test, *I*-squared (%)[a]	Heterogeneity test, *p*-value[a]
Type A/B	All ages	7 (6–8)	207	194,931	97	<0.001
	<1 year	3 (4–18)	5	3291	85	<0.001
	<5 year	0.8 (0.1–5)	4	962	92	<0.001
	<18 year	2 (0.8–4)	24	15,229	56	0.05
	≥18 year	8 (6–10)	38	20,824	84	<0.001
	≥50 year	12 (6–22.5)	12	10,152	56	0.05
Type A (all subtypes)	All ages	6 (5–6.5)	133	98,545	94	<0.001
	<1 year	5 (0.7–25)	2	18	91	<0.001
	<5 year	1 (0.1–8)	3	775	89	<0.001
	<18 year	1 (0.1–8)	3	775	87	<0.001
	≥18 year	10 (8–13.5)	21	5735	92	<0.001
	≥50 year	16 (3–51)	6	7186	56	0.05
Type A (subtype H1N1)	All ages	5.5 (4–7)	84	88,603	97	<0.001
	In ICU cases	25 (15.5–37.6)	8	2838	91	<0.001
	<1 year	4.5 (0.3–45)	1	10	0	1
	<5 year	–	–	–	–	–
	<18 year	1.5 (0.6–40)	10	3945	94	<0.001
	≥18 year	5.5 (3–8)	9	1105	40	<0.01
	≥50 year	17.5 (12–25.5)	2	120	96	<0.001
Type A (subtype H3N2)	All ages	1.7 (0.2–15)	4	68,579	87	<0.001
	<1 year	5 (0.7–28)	2	17	8	0.1
	<5 year	–	–	–	–	–
	<18 year	1.5 (0.6–4)	10	3945	9	<0.001
	≥18 year	2.5 (4–14)	4	825	65	0.003
	≥50 year	–	–	–	0	0.4
Type A (subtype H5N1)	All ages	42 (29–56)	5	146	56	0.05
	<1 year	–	–	–	–	–
	<5 year	–	–	–	–	–
	<18 year	77 (48–92)	1	13	87	<0.001
	≥18 year	40 (28–51)	1	67	87	<0.001
	≥50 year	–	–	–	–	–
	All ages	30 (25.6–35)	11	1018	52	0.02
Type A (subtype H7N9)	All ages	2 (1–5)	4	291	0	0.5
Type A (non-H1N1)	All ages	3 (2–4)	13	2812	87	<0.001
Type B	<1 year	–	–	–	–	–
	<5 year	–	–	–	–	–
	<18 year	2.5 (0.7–7.6)	3	1550	53	0.1
	≥18 year	–	–	–	–	–
	≥50 year	2.5 (0.7–7.6)	3	1550	89	<0.001

Abbreviation: ICU, intensive care unit.

[a]Greater than 50% is considered high heterogeneity, less than 50% is considered low heterogeneity. A low *p*-value (<0.05) is consistent with high heterogeneity.

TABLE 4 Meta-analysis on laboratory features for confirmed patients with COVID-19

		COVID-19			Influenza type A			Influenza type B		
	Normal range	Mean (CI 95%)	Patient *N*	Study *N*	Mean (CI 95%)	Patient *N*	Study *N*	Mean (CI 95%)	Patient *N*	Study *N*
Leucocytes (WBCs)	3.5–9.5	6.3 (× 10^9 per L) (5.1–7.5)	9268	62	6.4 (× 10^9 per L) (6.4–6.5)	16,962	48	7.4 (× 10^9 per L) (6.2–606)	940	9
Increased	–	13.3 (%)	–	–	16 (%)	–	–	10.5 (%)	–	–
Decreased	–	26 (%)	–	–	19 (%)	–	–	23 (%)	–	–
Neutrophils	1.8–6.3	4 (× 10^9 per L) (3–8.5)	8192	47	4.9 (4.6–5.2)	8718	16	4.8 (4.5.5)	561	5
Increased	–	–	–	–	–	–	–	–	–	–
Decreased	–	–	–	–	10 (%)	–	–	–	–	–
Lymphocytes	1.1–3.2	1.13 (× 10^9 per L) (0.9–1.2)	10,185	61	1.3 (× 10^9 per L) (1.1–1.4)	8820	24	1.5 (× 10^9 per L) (0.7–2.2)	499	6
Decreased	–	62.5 (%)	–	–	49 (%)	–	–	–	–	–
Platelets	125–350	186.5 (× 10^9 per L) (179–198)	6356	39	192 (× 10^9 per L) (187–199)	10,792	29	179 (× 10^9 per L) (159–199)	350	4
Decreased	–	13 (%)	–	–	24 (%)	–	–	16 (%)	–	–
Increased	–	28.5 (%)	–	–	10 (%)	–	–	3.5 (%)	–	–
CRP	0–0.5	29.6 (mg/L) (16.7–42.5)	1054	26	22.8 (mg/L) (22–35)	5237	14	32.4 (mg/L) (28–35)	287	3
Increased	–	81 (%)	–	–	62 (%)	–	–	43 (%)	–	–
Haemoglobin	130–175	119 (g/L) (106–132)	3062	37	–	–	–	–	–	–
ESR	0–15	28 (mm/h) (18–37)	1149	11	21 (mm/h) (13–29)	3209	8	15 (mm/h) (3–27)	241	2
Albumin	40–55	36.8 (g/L) (24.5–46)	1045	11	–	–	–	–	–	–
Decreased	–	80%	–	–	–	–	–	–	–	–
Interleukin-6	0.0–7	7.9 (mg/ml) (6.8–8.6)	99	2	–	–	–	–	–	–
Increased	–	52%	–	–	–	–	–	–	–	–
LDH	120–250	280 (268–294)	1783	9	–	–	–	–	–	–
Increased	–	70.3 (%)	–	–	–	–	–	–	–	–

Note: Increased or decreased refers to values above or below the normal range.

Abbreviations: CRP, C-reaction Protein; ESR, erythrocyte sedimentation rate; WBCs, white blood cells.

with COVID-19 infection, fatigue, sputum production and myalgia (muscle soreness) were the next most frequent clinical symptoms, while diarrhoea, rhinorrhoea, nausea and vomiting were less frequent. Within the 113,818 confirmed influenza type A patients, the next most frequent clinical manifestations were fatigue, sore throat, coryza, dyspnoea, rhinorrhoea, sputum production, chills, myalgia, pneumonia and headache.

Sore throat was less common in COVID-19 patients (11.5%), in comparison to influenza type A (49%) and influenza type B (38%). Likewise, rhinorrhoea was less common in COVID-19 patients (9.3%), in comparison to influenza type A (44.5%) and influenza type B (49%), as well as nausea and vomiting were less common in COVID-19 (6%), in comparison to influenza type A (20%) and influenza type B (20%). On the other hand, fatigue was one of the most common clinical symptoms in influenza type A (60%), in comparison to COVID-19 (27%) and influenza type B (21%). Dyspnoea was another less common clinical symptom in COVID-19 (15%), in comparison to influenza type A (45.5%) and influenza type B (33%). Therefore, these clinical symptoms may help in first screening and distinguishing these respiratory viral infections from each other.

Our analysis indicated a history of recent travel or contact with endemic populations, contact history with another person with respiratory symptoms and being a healthcare worker were common risks amongst COVID-19 confirmed cases. These data indicate, in coronavirus outbreaks, isolating infected individuals is one of the most important ways of controlling transmission.

ARDS (31.5%) was the most common amongst patients of influenza type A in comparison to COVID-19 (26.6%) and influenza type B

(0.8%). In addition, the most common comorbid chronic condition for COVID-19 and influenza type A were hypertension (20%), and diabetes (19%)for influenza type B, as well as viral (24%) and fungi (20%) co-infection occurred more frequently in influenza type B in comparison to two other virus infections, which indicate influenza type B may be pathogenic in people who have other infections.

We find that most of the patients with COVID-19 had abnormal chest radiology (84%), in comparison to influenza type A (57%) and B (33%). GGO and consolidation in COVID-19 patients being more frequent than in influenza type A and B patients. Radiologic findings and clinical symptoms such as sore throat indicated that the virus in COVID-19 patients targets the lower respiratory system, while the upper respiratory system is more involved in influenza infections in comparison to COVID-19.

Our analysis showed that the incubation period in COVID-19 (6.4 days estimated from present literature to date) was more extended than influenza type A (3.4 days). Likewise, the duration of hospitalization in COVID-19 patients (14 days) is longer than influenza type A (6.5 days) and influenza type B (6.7 days). These results suggest that the flu virus may show clinical signs earlier than the COVID-19, and flu patients are discharged sooner than COVID-19 patients from the hospital. Moreover, the hospital discharged rate of COVID-19 (57.5%) is lower in comparison to influenza type A (82%) and influenza type B (87.5%) patients.

Our analysis showed that the mortality rates of COVID-19, influenza types A and B are 6.5%, 6% and 3%, respectively. Based on WHO reports on 26 April 2020, out of 2804, 796 COVID-19 confirmed cases and 193,710 cases died (6.9%) around the world, which is similar to our result. Among influenza type A, the mortality rates in subtypes H5N1 (42%) and H7N9 (30%) were higher than subtypes H1N1 (5.5%), H3N2 (1.7%) and non-H1N1 (2%). The influenza mortality rate was associated with different age groups, in which a higher mortality rate is shown in people with ≥50-year-old ages (12%) in comparison to other age groups. These results indicated that older people are at risk of death from the flu. However, subtype H5N1 is fatal and life threatening for all age ranges.

Several limitations of this study exist. Publication bias and study heterogeneity are unavoidable in this type of study. Therefore, it should be considered when interpreting the outcomes of the reports and our final data-set. Furthermore, this study likely overestimates disease severity due to a lack of screening of asymptomatic or mildly symptomatic individuals and subsequent publication bias related to these factors. Likely, many infected persons have not been detected, thus falsely elevating the rates of hospitalization and mortality compared to the milder symptomatic population. Whether this issue is the same for all viruses evaluated here is unknown. The lower quality analysis and reporting in some of the included publications is another limitation of the study. To prevent language bias, we included reports in languages other than English.

Additionally, we searched for a variety of sites and databases to prevent Internet platform bias. Using Egger's regression test, we did not find significant publication bias. Journal bias is an issue facing those who carry out a meta-analysis, yet it does not usually affect the general conclusions.[33] However, we cannot reject the occurrence of other biases in this study, such as choice bias, since several journals are not indexed in Embase, Scopus, PubMed, Web of Science and the Cochrane library, and unpublished data from some regions of the world.

5 | CONCLUSIONS

The results showed that despite the development of respiratory disease and similar transmission methods, COVID-19 and influenza had many differences in terms of involvement and severity of the pulmonary injury, mortality rate, laboratory finding and clinical symptoms. Due to the high transmissibility and the lack of effective medication or vaccine for COVID-19, timely detection of this viral infection and distinguishing from influenza are very important.

CONFLICT OF INTEREST

The authors have declared that no conflict of interests.

AUTHOR CONTRIBUTIONS

Conceived and designed the study: Ali Pormohammad, Juan-Pablo Idrovo and Saied Ghorbani; comprehensive research: Saied Ghorbani, Alireza Khatami, Mohammad Hossein Razizadeh, Ehsan Alborzi and Ali Pormohammad; analysed the data: Ali Pormohammad; wrote and revised the paper: Ali Pormohammad, Saied Ghorbani, Juan-Pablo Idrovo, Raymond J. Turner, Alireza Khatami, Mohammad Hossein Razizadeh, Ehsan Alborzi and Mohammad Zarei; participated in data analysis and manuscript editing: Ali Pormohammad, Saied Ghorbani, Juan-Pablo Idrovo, Raymond J. Turner, Alireza Khatami, Mohammad Hossein Razizadeh, Ehsan Alborzi and Mohammad Zarei.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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